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Efficacy of HPV Vaccine: Intralesional Versus Intramuscular Administration in The Treatment of Recalcitrant Warts

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Conflict of interest: Nil

Abstract

Background: Human papillomavirus (HPV)-associated warts are common skin disorders that commonly recur despite conventional treatment. Immunotherapeutic approaches became promising alternatives that target viral infection by enhancing host immune responses. Literature shows therapeutic role for HPV vaccines given through intramuscular or intralesional routes in patients with recalcitrant warts.

Aim: To compare the efficacy and safety of intramuscular and intralesional HPV vaccine administration in the treatment of recalcitrant HPV-associated warts.

Materials and Methods: This comparative interventional study was done among 80 patients with recalcitrant HPV-associated warts attending the Department of Dermatology of a tertiary care teaching hospital. Patients were allocated into two groups of 40 each. Group A patients received quadrivalent HPV vaccine through the intramuscular route, Group B patients received intralesional quadrivalent HPV vaccine. Clinical response, time to improvement, recurrence rates, and adverse events were assessed.

Results: 80 patients completed the study. Complete clearance was achieved in 24 patients in the intramuscular group and 31 patients in the intralesional group. Average time to improvement was significantly shorter in the intralesional group compared to intramuscular group. Recurrence occurred in 4 patients in the intramuscular group and 2 patients in the intralesional group. Both treatment modalities were well tolerated, and no serious adverse events were seen.

Conclusion: Both intramuscular and intralesional HPV vaccine administration were effective in the treatment of recalcitrant HPV-associated warts. But intralesional administration showed more clearance rate, earlier clinical response, and lower recurrence rates along with acceptable safety profile. Intralesional HPV vaccine immunotherapy may represent a promising therapeutic option for patients with treatment-resistant HPV-associated warts.

Keywords: Human papillomavirus, HPV vaccine, intralesional immunotherapy, intramuscular vaccination, recalcitrant warts, therapeutic vaccine.

Introduction

Human papillomavirus (HPV) infection is one of the most common viral infections affecting humans worldwide. HPV belongs to the family Papillomaviridae and includes large group of double-stranded DNA viruses that show tropism for squamous epithelial tissues. More than 200 HPV genotypes have been found. These are classified into low-risk and high-risk categories according to their oncogenic nature. Low-risk HPV types like HPV-6 and HPV-11 are commonly associated with benign lesions like cutaneous and anogenital warts. High-risk types like HPV-16 and HPV-18 are strongly associated with cervical cancer and several other anogenital and oropharyngeal malignancies.[1]

Cutaneous warts are benign proliferative lesions occuring due to infection of keratinocytes by HPV. They represent a common dermatological problem, affecting approximately 7–12% of the general population and up to 20% of school-aged children.[2] The prevalence is more among patients with impaired cellular immunity, including organ transplant recipients and patients receiving immunosuppressive therapy. Spontaneous resolution occurs in most patients due to host immune responses, but many lesions persist for months or years and become resistant to treatment.[3]

Pathogenesis of HPV infection includes viral entry through micro-abrasions in the skin or mucosa. After infection of basal keratinocytes, the virus establishes itself within the epithelium and uses host cellular machinery for replication. Viral proteins interfere with normal immune recognition mechanisms, allowing HPV to evade host immune surveillance and persist for prolonged periods.[1] This immune evasion causes chronic infection and recurrence after treatment.

Conventional treatment modalities for warts are cryotherapy, electrocautery, radiofrequency ablation, surgical excision, laser therapy, salicylic acid preparations, trichloroacetic acid, and topical immunomodulators such as imiquimod.[4] In spite of available therapies, none has showed universal effectiveness. Recurrence rates are more, and repeated treatment sessions are commonly required. Many destructive therapies are associated with pain, scarring, pigmentary changes, and poor patient compliance.[4,5]

Immunotherapy stimulate cell-mediated immunity and eliminates visible lesions and latent viral infection.[6] Immunotherapeutic agents are Bacillus Calmette–Guérin vaccine, Candida antigen, purified protein derivative, measles-mumps-rubella vaccine, and HPV vaccines. These therapies showed varying degrees of success in patients with recalcitrant warts. The immune response plays vital role in the natural history of HPV infection. Regression of warts is believed to result primarily from activation of cell-mediated immunity rather than humoral immunity. Studies showed increased infiltration of CD4+ and CD8+ T lymphocytes in regressing lesions, with increased production of cytokines like interferon-gamma and interleukin-2.[3] Therapies that improve cellular

immune responses may improve treatment outcomes in persistent HPV infection.

Introduction of prophylactic HPV vaccines changed the landscape of HPV prevention. Currently available vaccines include bivalent, quadrivalent, and nonavalent formulations based on recombinant virus-like particles derived from the HPV L1 capsid protein. These vaccines have showed excellent efficacy in preventing HPV infection and reducing the incidence of cervical intraepithelial neoplasia and anogenital warts.[7,8] Vaccination may increase antigen presentation by dendritic cells, stimulate Th1-mediated immune responses, increase cytokine production, and activate cytotoxic T lymphocytes.[6,9]

Intramuscular administration is the standard route for prophylactic HPV vaccination. Several case reports, case series, and observational studies have showed regression of recalcitrant warts following intramuscular vaccination.[10] The therapeutic effect occurs due to induction of systemic immunity and enhancement of HPV-specific cellular immune responses.

Intralesional administration of HPV vaccine is a novel therapeutic approach. Direct injection of vaccine antigens into wart tissue enhance local immune activation by exposing antigen-presenting cells to viral antigens within the lesion microenvironment.[11]

Nofal et al. compared intralesional and intramuscular administration of the bivalent HPV vaccine in patients with recalcitrant common warts. There is favorable outcome with both modalities but authors suggested that intralesional administration may provide superior clinical responses in selected patients.[12] Recent reviews showed growing evidence supporting therapeutic HPV vaccination.[13-15]

Aim: To compare the efficacy and safety of intramuscular and intralesional HPV vaccine administration in patients with recalcitrant HPV-associated warts.

Materials and Methods

Study Design

This comparative interventional study was done in the Department of Dermatology, Venereology and Leprosy of a tertiary care teaching hospital over a period of 12 months- May 2025 to May 2026

Study Population

Patients presenting with clinically diagnosed recalcitrant HPV-associated warts were screened for eligibility.

Recalcitrant warts were defined as lesions persisting for more than six months despite treatment with at least one conventional therapeutic modality.

Sample Size

80 patients were enrolled in the study and divided into two groups of 40 patients each.

Inclusion Criteria

- Age between 18 and 60 years.
- Presence of cutaneous or anogenital warts.
- Disease duration greater than six months.
- Failure of previous conventional treatment.
- Provision of written informed consent.

Exclusion Criteria

- Pregnancy or lactation.
- Immunocompromised states.
- History of hypersensitivity to HPV vaccine
- Active systemic infection.
- Recent treatment for warts within the previous four weeks.
- Concurrent immunosuppressive therapy.

Study Groups: Patients were divided by randomization.

Group A: Intramuscular HPV Vaccine Group

Forty patients received quadrivalent HPV vaccine through intramuscular injection according to the standard vaccination schedule.

Patients received 0.5 mL of quadrivalent HPV vaccine intramuscularly in the deltoid region

Group B: Intralesional HPV Vaccine Group

Forty patients received intralesional quadrivalent HPV vaccine injected into the largest wart at predetermined treatment intervals. Patients received 0.1–0.3 mL of quadrivalent HPV vaccine injected into the base of the largest wart under aseptic precautions.

Clinical Evaluation

Baseline assessment included demographic data, duration of disease, number of lesions, anatomical site, previous treatments, and wart morphology. Clinical photographs were obtained before treatment and during follow-up visits.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using SPSS version 22. Quantitative variables were expressed as mean ± standard deviation, qualitative variables were expressed as frequencies and percentages. Statistical significance was determined using student t test for numerical parameters and chi square test for categorical parameters with $p < 0.05$ considered significant.

Written informed consent was obtained from all participants before enrollment.

Results

Baseline Characteristics

80 patients completed the study. Forty patients were allocated to the intramuscular HPV vaccine group (Group A) and forty patients to the intralesional HPV vaccine group (Group B).

Table 1: Baseline Demographic Characteristics

Variable	Intramuscular Group (n=40)	Intralesional Group (n=40)	p-value
Mean age (years)	31.8 ± 8.6	32.4 ± 9.1	0.77
Male, n (%)	24 (60.0%)	23 (57.5%)	0.82
Female, n (%)	16 (40.0%)	17 (42.5%)	
Mean disease duration (months)	14.6 ± 5.4	15.1 ± 5.7	0.78
Previous cryotherapy, n (%)	28 (70.0%)	30 (75.0%)	0.62
Previous topical therapy, n (%)	22 (55.0%)	24 (60.0%)	0.65

No statistically significant differences were seen between the two groups at baseline. So, both groups are comparable at baseline.

Clinical Characteristics of Warts Common warts are most commonly found.

Graph 1: Distribution of Wart Types

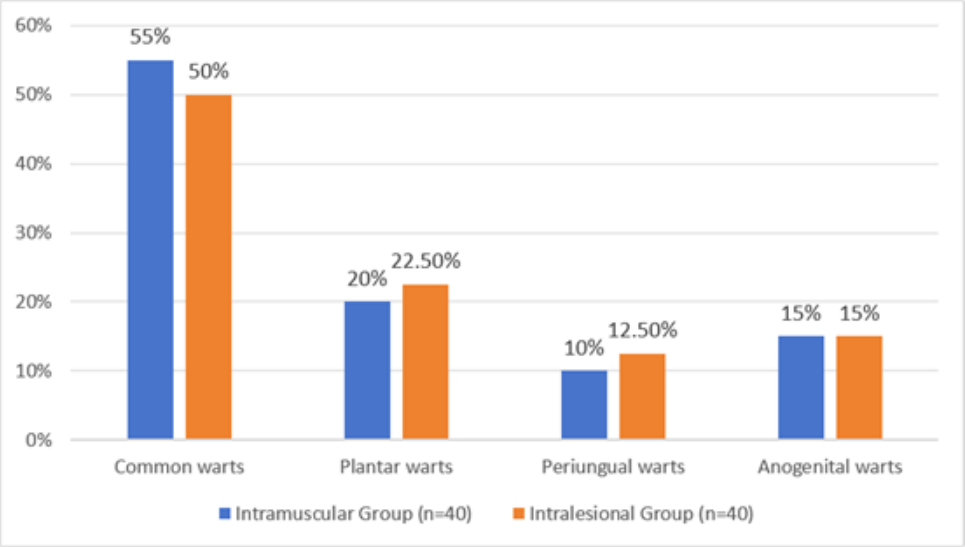

Table 2: Clinical Outcomes at 24 Weeks

Complete clearance was seen among 24 patients of group A and 31 patients of group B

Outcome	Intramuscular Group (n=40)	Intralesional Group (n=40)	p-value
Complete clearance, n (%)	24 (60.0%)	31 (77.5%)	0.091
Partial response, n (%)	10 (25.0%)	6 (15.0%)	—
No response, n (%)	6 (15.0%)	3 (7.5%)	—
Overall response, n (%)	34 (85.0%)	37 (92.5%)	0.289
Overall outcome distribution	—	—	0.23

Graph 2: Time to Complete Clearance

Time to complete clearance was less in intralesional group compared to intramuscular group(P=0.012)

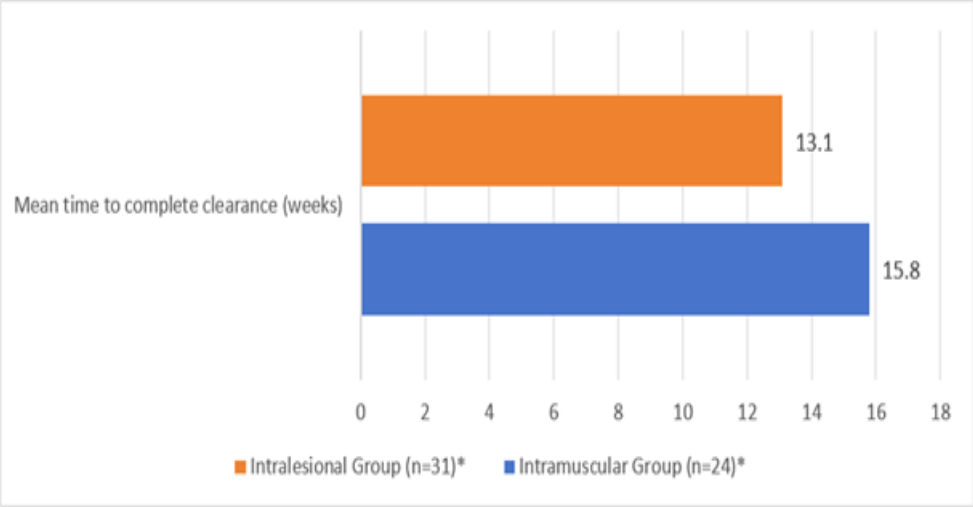

Table 3: Adverse Effects Observed During Treatment

There is no significant difference between adverse effects seen between two groups.

Both treatment modalities were well tolerated. Injection-site pain was the most common adverse effect and was reported more commonly in the intralesional group

Adverse Effect	Intramuscular Group (n=40)	Intralesional Group (n=40)
Injection-site pain	8 (20.0%)	15 (37.5%)
Erythema/swelling	5 (12.5%)	9 (22.5%)
Mild fever	4 (10.0%)	3 (7.5%)
Flu-like symptoms	3 (7.5%)	2 (5.0%)
Any adverse effect	16 (40.0%)	22 (55.0%)
p-value	0.18	

Table 4: Recurrence Rates

There is no significant difference in recurrence rate in between two groups. These patients(n=24 and n=31 in both groups) had complete clearance and assessed for recurrence rates.

Parameter	Intramuscular Group (n=24)	Intralesional Group (n=31)	p-value
Recurrence	4 (16.7%)	2 (6.5%)	0.387
No recurrence	20 (83.3%)	29 (93.5%)	

Discussion

The present study assessed and compared the therapeutic efficacy of intramuscular and intralesional HPV vaccine administration in 80 patients with recalcitrant HPV-associated warts. The findings showed that both routes were effective in inducing clinical improvement; but, intralesional administration produced superior therapeutic outcomes in terms of complete clearance, earlier clinical response, and lower recurrence rates.

In the present study, complete clearance was achieved in 77.5% of patients receiving intralesional HPV vaccine compared with 60.0% of patients receiving intramuscular vaccination. More clearance rate in the intralesional group suggests more therapeutic efficacy associated with local vaccine administration. Similar findings are reported by Nofal et al., who compared intralesional and intramuscular bivalent HPV vaccine therapy and found better outcomes among patients receiving intralesional treatment.[8] Superior response may be explained by direct stimulation of local antigen-presenting cells within wart tissue. Injection of vaccine antigens into the lesion promotes recruitment of macrophages, dendritic cells, and cytotoxic T lymphocytes, causing enhanced recognition and destruction of HPV-infected keratinocytes.[11,12] These local immunological events may induce systemic immune responses that target distant untreated lesions.

Overall response rate in the present study was 92.5% in the intralesional group and 85.0% in the intramuscular group. Bar-Ilan et al. Reported more rates of wart regression following intralesional HPV vaccine administration and showed its usefulness in patients who

had failed conventional treatments.[10] Hammad et al. showed significant therapeutic responses among patients receiving intralesional HPV vaccine and identified several factors associated with successful outcomes.[9]

An important finding of the present study was the significantly shorter time to clinical improvement observed in the intralesional group. Patients receiving intralesional therapy showed visible improvement after a mean duration of 6.8 ± 1.9 weeks compared with 10.2 ± 2.8 weeks in the intramuscular group. Earlier clinical response is clinically advantageous because it reduces disease burden, improves patient satisfaction, and may enhance treatment adherence. The accelerated response associated with intralesional administration may reflect immediate exposure of local immune cells to vaccine antigens, resulting in rapid activation of cell-mediated immune pathways.[9]

Analysis according to wart type demonstrated the highest clearance rates among patients with common warts in both treatment groups. Complete clearance of common warts was achieved in 90% of patients receiving intralesional therapy compared with 68.2% of those receiving intramuscular vaccination. Similar trends have been reported in previous studies, which have suggested that common warts may respond more favorably to immunotherapeutic interventions than plantar or periungual lesions.[2,13]

Recurrence remains an important concern in the management of HPV-associated warts because conventional destructive therapies frequently fail to eliminate latent infection. In the present study, recurrence occurred in 16.7% of patients in the intramuscular group compared with 6.5% of patients in the intralesional group during six months of follow-up. Though this difference was not statistically significant, the lower recurrence rate observed with intralesional therapy may indicate the development of a more robust and durable immune response. Previous studies have similarly reported low recurrence rates after HPV vaccine immunotherapy.[12,13]

Local erythema and swelling were seen more commonly among patients receiving intralesional therapy, whereas mild systemic symptoms like fever and fatigue occurred more commonly after intramuscular administration. No serious adverse events were encountered. These findings are consistent safety profile of HPV vaccines reported in large clinical trials and post-marketing surveillance studies.[7,8]

The findings of the present study support informing prophylactic HPV vaccines possess therapeutic and preventive properties. Unlike conventional destructive methods, HPV vaccine immunotherapy addresses ummunological basis of persistent HPV infection and may provide systemic protection against recurrence.[6,9]

Several limitations should be acknowledged. The study was conducted at a single center and involved a relatively modest sample size of 80 patients. HPV genotyping was not performed, and immunological markers were not evaluated. Furthermore, follow-up was limited to six months. Larger multicenter randomized controlled trials with longer follow-up periods are required to confirm these findings and establish standardized treatment protocols.

Conclusion

The complete clearance rate seen in the intralesional group (77.5%) was more than that achieved with intramuscular vaccination (60%). This implies that direct administration of vaccine antigens into wart tissue may enhance local and systemic immune responses against HPV-infected keratinocytes. The findings of the present study suggest that intralesional HPV vaccine

administration may be a more effective immunotherapeutic option than intramuscular vaccination for patients with recalcitrant HPV-associated warts. More multicenter randomized controlled trials with larger sample sizes, longer follow-up period, and evaluation of immunological markers are required to confirm these findings.

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