RESEARCH ARTICLE

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Post-Authorization Safety Study of Papilloguard (A Domestically Manufactured Bivalent (16,18) HPV Vaccine in Iran

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Abstract

Background: In recent years, various vaccines, including Papilloguard, have been introduced to prevent transmission of this virus. This vaccine has shown good immunogenicity and efficacy profile in phase III study; however, its safety remains controversial. This study aimed to investigate the complications and adverse events associated with the Papilloguard vaccine in the Iranian population. **Methods:** In this survey study, 1,028 volunteers (690 (67.1%) female and 338 (32.9%) males, mean age 33.8±7.01), who had received the Papilloguard vaccine and whose basic information was recorded in the Papilloguard vaccine registration system by call center team of Arta Pharmed Company (Tehran, Iran) were examined. Cumulative vaccine-related complications were assessed and recorded by Arta Pharmed Company's call center team 7 days, 1 month, and 6 months after receiving each dose of vaccine during the 6 months following vaccination. Patient evaluations were conducted over the phone. Any complication leading to hospitalization or requiring medical interventions was defined as a serious complication. **Result:** The cumulative incidence of at least one complication immediately after injection, 7 days, 1 month, and 6 months after injection was reported in 272 (26.5%), 101 (9.8%), 74 (7.2%), and 29 (2.8%) of the participants, respectively. Post-injection pain was the most common complication after vaccination, 227 (22.1%). The cumulative incidence of injection site pain 7 days, 1 month, and 6 months after injection was 8.4%, 5.7%, and 0.7%, respectively. In terms of severity of complications, complications were reported as mild in 253 (24.6%), moderate in 15 (1.5%), and severe in 4 (0.4%) recipients. Only 0.4% of recipients experienced severe complications. **Conclusion:** In a mid-term follow-up, in the Iranian population, Papilloguard vaccine had few side effects and was well tolerated. Papilloguard vaccine can be included in national vaccination guidelines for the prevention of HPV and its consequences.

Keywords: Human papillomavirus, vaccination, side effects, Iran, Papilloguard

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Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted viruses worldwide [1, 2]. According to the latest studies, the reported annual incidence rate is typically between 100 and 200 new cases per 100,000 adult population [3]. The global prevalence of HPV in women, excluding cervical disorders, is estimated to be 11–12%, with the first HPV peak observed at ages 25 years and younger and the second HPV peak at around age 45 years [4, 5].

More than 40 types have been identified in the genital area, the majority of which are classified as low-risk or high-risk for causing cancer [6]. Fifteen high-risk HPV types have been identified, with types 16 and 18 responsible for about 70 % of all cervical cancer cases and considered the most common HPV types worldwide [7, 8]. Accurate statistics on the prevalence of HPV in Iran are not available. However, according to the latest meta-analyses, the prevalence of HPV infection in the population of healthy women and women with cervical cancer was 9.4% and 77.4%, respectively, and the predominant genotype in both groups was HPV-16 [9, 10].

The World Health Organization (WHO) has recently highlighted the urgent need for global collaboration aimed at eradicating cervical cancer by 2030 [11]. In this context, the WHO emphasizes that primary prevention through vaccination should be prioritized over cancer screening. This proactive approach not only addresses cervical cancer but also strengthens communities against other HPV-related cancers. These include oropharyngeal, anal, penile, vulvar, vaginal, and to some extent, breast cancer, which together accounted for about 5% of the global cancer burden in 2018 [12].

Vaccination is a cost-effective method for preventing diseases caused by microbial and viral agents, including HPV [13, 14]. The primary goal of HPV vaccination is to reduce the incidence of cervical cancer and its precursor lesions. A secondary goal is to reduce the incidence of HPV-related cancers and associated benign conditions [14-

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16]. The World Health Organization strongly recommends vaccination of girls over the age of 9, especially before their first sexual experience [17]. In the world, three types of vaccines have been produced against this virus based on the serotypes present in the vaccine. All vaccine forms contain HPV-like virus particles from types 16 and 18, and all vaccines contain virus particles and components, not live or weakened viruses themselves, which is why few side effects have been recorded for them so far [13, 18]. The initial vaccine that received approval, Gardasil, has been substituted with Gardasil9, which demonstrates an overall cervical cancer prevention rate that is not less effective than that of the rival HPV vaccine, Cervarix [13, 19-20].

The long- and medium-term effects of vaccines and drugs administered concurrently with other drugs in the community are very different from those reported in randomized clinical trial studies. Therefore, the generalizability of results from RCTs to the clinical community is very limited. Therefore, health policymakers in many countries have initiated continuous monitoring and surveillance of drug use and efficacy in routine care systems in the community [21-23]. Regular monitoring of vaccines and drugs to assess adverse effects and efficacy at the community level is considered a very important part of drug surveillance after drug approval and market entry, which is carried out by the Food and Drug Administration (FDA) or other drug regulatory agencies [24, 25].

Papilloguard vaccine is a bivalent HPV (16/18) vaccine, Papilloguard (Noyan Pajoohan Biopharma, Tehran, Iran), whose immunogenicity profile and efficacy have been confirmed in a phase III clinical trial study [26]. However, its medium- and long-term safety at the community level remains uncertain. This survey aimed to investigate mild and serious mid-term adverse events associated with the Papilloguard vaccine in the Iranian community.

Materials and Methods

This study was approved by the Ethics Committee of the Iran University of Medical Sciences (Ethical code: IR.IUMS.FMD.REC.1403.140).

In this survey study, the data of 1451 participants who had received the Papilloguard vaccine and the information about the vaccine and recipients was recorded by the call center team of Arta Pharmed Company (Tehran, Iran). The recipients of the Papilloguard vaccine were injected by visiting the vaccination centers after scanning the QR code on the vaccine box and registering it in the Papilloguard vaccine registry system. One thousand twenty-nine vaccine recipients were included in this study. Patient sampling was performed consecutively from all referrals whose information was recorded in the Papilloguard vaccine system.

Volunteers receiving Papilloguard vaccine received a 0.5 mL prefilled syringe containing 20 µg VLP16 and 20 µg VLP18. Intramuscular injection was performed in the deltoid muscle of the non-dominant hand.

Inclusion criteria included an age range of 18 to 50 years, non-pregnant women, and informed consent to participate in the study. Women with a history of HPV vaccine (Gardasil), receiving other viral vaccines in the past 1 month and a history of severe allergic reaction (anaphylaxis) or any other reaction to viral vaccines HPV vaccines were defined as exclusion criteria. Complications related to vaccine administration were recorded in telephone follow-ups immediately after injection, 7 days, one month, and 6 months after vaccination.

Registration of the vaccine and follow-up of the recipients were carried out as follows

• Logging into the registry (day zero to minus 3 days)

• Scanning the QR code on the vaccine box and logging into the Papilloguard registry

• Entering basic data into the registry

Visit zero (half an hour after injection):

• Injection of Papilloguard vaccine into the deltoid muscle of the non-dominant hand

• Monitor the volunteer for up to 30 minutes after injection

• Reporting of adverse events and recording of side effects

Visits 1, 2, 3, and 4 were conducted by telephone to follow up on possible events 1, 7, 30 days, and 6 months after the vaccine injection, respectively. Side effects were reported cumulatively over the 6 months after injection.

Data collection

Patient data was collected after the patient visit and assessment using a checklist. Demographic data included (age, gender, body mass index(BMI), Previous history of HPV infection, and comorbidity (hypertension, diabetes, thyroid, or hyperglycemia). Outcomes included the incidence of Medically Attended adverse Events (MAEs), the incidence of Serious Adverse Event)SAEs(, the incidence of Potential Immune-Mediated Diseases (pIMDs) (neuroinflammatory diseases such as Bell's palsy, autoimmune diseases (multiple sclerosis(and metabolic diseases (autoimmune thyroiditis)) during the study period (6 months after the last dose of vaccine), the incidence of local and systemic solicited adverse drug reactions, local or general solicited adverse events (pain, redness, swelling at the injection site, fever, arthralgia, fatigue, gastrointestinal symptoms (nausea, vomiting, diarrhea, and pain), headache, myalgia, rash, and urticaria), the number of unsolicited adverse events, and medication errors (MEs) during vaccine administration.

The pIMDs are presented separately in supplement 1, Table 1. SAEs were defined as any adverse event that resulted in death, life-threatening, requiring hospitalization or prolongation of hospitalization, disability, or congenital malformation or disability. Monitoring, evaluation, and recording of side effects were carried out independently by experts independent of the pharmaceutical company.

Statistical analysis

Data were analyzed using SPSS version 22 statistical software. Descriptive statistics and central indices (Mean and SD) were used to estimate the mean and median in the two groups. All AEs were reported as numbers and percentages. Adverse events were classified by System

Organ Class separately for serious adverse events (SAEs) and medically necessary adverse events (MAEs). The association between the incidence of complications and baseline characteristics of the participants was assessed using Spearman's correlation coefficient. A p-value of less than 0.05 was considered statistically significant.

Results

One thousand twenty-nine recipients of the Papilloguard vaccine completed the study. The mean age of recipients was 33.8±7.01 years (age range 19 to 47 years). 690 (67.1%) were female and the rest were male. 131 (12.7%) patients had a history of prior HPV infection. 191 (18.6%) patients had a history of concurrent underlying diseases. The demographic characteristics of the patients at the time of Papilloguard vaccine administration are reported in Table 1.

Incidence, type, and severity of complications at zero time

1028 participants were assessed for complications immediately after injection. At least one post-injection complication was reported in 272 (26.5%) participants immediately after Papilloguard vaccination. Injection site pain was the most common complication after vaccination and was reported in 227 (22.1%) recipients. Fever was reported in 11 (1.1%) patients. The incidence of fatigue was 0.5%. The incidence of medical errors during vaccination was 0.6%. In terms of severity of complications, complications were reported as mild in 253 (24.6%) patients, moderate in 15 (1.5%), and severe in 4 (0.4%) recipients. No serious complications occurred immediately after injection. The majority of complications resolved without intervention, and the need for analgesics or treatment to reduce complications (mostly pain) was reported in only 24 (2.3%) patients. The incidence, type, and severity of complications at time zero are reported in Table 2.

Table 1. Baseline Characteristics of Recipients at the Time of Vaccination

Variable	1029 participants
Age (Year)	33.8±7.01
BMI (Kg/m^2)	25.4±2.9
Sex, N (%)	
Female	690 (67.1%)
Male	339 (32.9%)
HPV history	
Yes	131 (12.7%)
No	898 (87.3%)
Married Status, N (%)	
Married	374 (36.3%)
Unmarried	655 (63.7%)
Comorbidity, N (%)	
Yes	191 (18.6%)
No	891 (81.4%)

Incidence, type, and severity of complications 7 and 30 days after injection

1028 participants were evaluated for complications 7 days after injection. At least one complication was reported 7 days after injection in 101 (9.8%) participants. Injection site pain was the most common complication after vaccination and was reported in 86 (8.4%) recipients. Fever was reported in 3 (3%) patients. In terms of severity, complications were reported as mild in 89 (8.7%) patients, moderate in 8 (0.8%) and severe in 4 (0.4%) recipients. No serious complications occurred 7 days after injection. The majority of complications resolved without intervention, and the need for analgesics or treatment to reduce complications (mostly pain) was reported in only 17 (1.7%) patients (Table 3).

At least one post-injection event was reported in 74 (7.2%) participants one month after Papilloguard vaccination. Injection site pain was the most common event one month after vaccination, reported in 59 (5.7%) recipients. In terms of severity, the event was reported as mild in 60 (5.58%) patients and severe in 4 (0.4%) recipients. No event occurred one month after

Table 2. Incidence and Type of Complications at Zero Time

Variable	1028 participants
Complication, N (%)	
No	756 (73.5%)
Yes	272 (26.5%)
AE type, N (%)	
No	756 (73.5%)
Alopecia	1 (0.1%)
Breast contusion	1 (0.1%)
Diarrhoea	2 (0.2%)
Dizziness	1 (0.1%)
Fatigue	5 (0.5%)
Fever	11 (1.1%)
Headache	3 (0.3%)
Hypersensitivity	1 (0.1%)
Injection site bruising	1 (0.1%)
Injection site erythema	1 (0.1%)
Injection site pain	227 (22.1%)
Injection site pruritus	3 (0.3%)
Injection site swelling	2 (0.2%)
Lethargy	1 (0.1%)
Medication error	6 (0.6%)
Menstrual disorder	1 (0.1%)
Myalgia	4 (0.4%)
Rhinitis	1 (0.1%)
Serious complication, N (%)	
No	1028 (100%)
Yes	0
Need for treatment and sedation, N (%)	
Yes	24 (2.3%)
No	1004 (97.7%)

Table 3. Incidence and Type of Complications 7 Days after Injection

Variable	1028 participants
Complication, N (%)	
No	927 (90.2%)
Yes	101 (9.8%)
AE type, N (%)	
No	927 (90.2%)
Diarrhoea	1 (0.1%)
Dizziness	1 (0.1%)
Fatigue	3 (0.3%)
Fever	2 (0.2%)
Headache	3 (0.3%)
Injection site pain	86 (8.4%)
Injection site swelling	1 (0.1%)
Myalgia	1 (0.1%)
Nausea	1 (0.1%)
Urticaria	1 (0.1%)
Vomiting	1 (0.1%)
Serious complication, N (%)	
No	1028 (100%)
Yes	0
Need for treatment and sedation, N (%)	
No	17 (1.7%)
Yes	1011 (98.3%)
Severity	
No	927 (90.2)
Mild	89 (8.7%)
Moderate	8 (0.8%)
Severe	4 (0.4%)

Table 4. Incidence and Type of Complications 30 Days after Injection

Variable	1028 participants
Complication, N (%)	
No	954 (92.8%)
Yes	74 (7.2%)
AE type, N (%)	
No	999 (97.2%)
Dizziness	2 (0.2%)
Fatigue	1 (0.1%)
Injection site pain	59 (5.7%)
Injection site swelling	4 (0.4%)
Menorrhagia	1 (0.1%)
Myalgia	4 (0.4%)
Nausea	1 (0.1%)
Urticaria	1 (0.1%)
Vomiting	1 (0.1%)
Serious complication, N (%)	
No	1028 (100%)
Yes	0
Need for treatment and sedation , N (%)	
Yes	15 (1.5%)
No	1013 (98.5%)
Severity	
No	954 (92.8)
Mild	60 (5.8%)
Moderate	10 (1%)
Severe	4 (0.4%)

the injection. The majority of events resolved without intervention, and the need for analgesics or treatment to reduce the event (mostly pain) was reported in only 15 (1.5%) participants. The incidence, type, and severity of complications 7 and 30 days after injection are reported in Table 4.

Incidence, type, and severity of complications six months after injection

At least one complication was reported six months after vaccination in 29 (2.8%) participants. In terms of severity, complications were reported as mild in 24 (2.4%) patients, moderate in 1 (0.1%) and severe in 4 (0.4%) recipients. Injection site pain was the most common complication six months after vaccination, reported in 7 (0.7%) recipients. Fever was reported in 5 (0.5%) patients. The incidence of fatigue was 0.4%. No serious complications occurred six months after vaccination. The majority of complications resolved without intervention, and the need for analgesics or treatment to reduce complications (mostly pain) was reported in only 8 (0.8%) patients (Table 5).

Six months after injection no significant relationship was observed between the incidence of complications with age (r=0.09, p: 0.27), BMI (r=0.05, p: 0.33), sex(r=0.08, p: 0.29), comorbidity(r=0.1, p: 0.11), and previous history of HPV(r=0.04, p: 0.41) (Table 6).

Discussion

The high prevalence of HPV and the high cost of quadrivalent and bivalent vaccines Gardasil as a highly effective and safe vaccine and the development of new bivalent and non-quadrivalent vaccines have provided the opportunity to replace new bivalent vaccines, including Papilloguard at the primary health level. The development and replacement of these vaccines at the community level requires regular evaluation of their safety and efficacy. Therefore, evaluating the effectiveness and estimating the side effects of these vaccines at the community level has become more critical than ever [27-29]. Therefore, the present study was conducted to investigate the safety of Papilloguard vaccine in 1028 recipients of this vaccine with an average age of 33 years. The results of this study can help health policymakers make decisions at the national level and also help physicians prescribe this vaccine with sufficient knowledge of its associated complications.

According to the results of this study, the majority of vaccine recipients in this study were women, and this difference in the frequency of the two sexes can be

Table 5. Cumulative Incidence and Type of Complications 6 Month after Injection

Variable	1028 participants
Complication, N (%)	
No	999 (97.2%)
Yes	29 (2.8%)
AE type, N (%)	
No	999 (97.2%)
Diarrhoea	1 (0.2%)
Dizziness	2 (0.2%)
Fatigue	4 (0.4%)
Fever	5 (0.5%)
Headache	1 (0.1%)
Hypersensitivity	1 (0.1%)
Injection site bruising	1 (0.1%)
Injection site erythema	1 (0.1%)
Injection site pain	7 (0.7%)
Injection site swelling	1 (0.1%)
Myalgia	2 (0.2%)
Nausea	1 (0.1%)
Urticaria	1 (0.1%)
Vomiting	1 (0.1%)
Serious complication, N (%)	
No	1028 (100%)
Yes	0
Need for treatment and sedation, N (%)	
Yes	8 (0.8%)
No	1020 (99.2%)
Severity	
No	999 (97.2)
Mild	24 (2.3%)
Moderate	1 (0.1%)
Severe	4 (0.4%)

Table 6. Relationship between Cumulative Incidence of Complications Six Months after Injection and Participant Characteristics

Variable	R coefficient	P value
Age (Year)	0.09	0.27
BMI (Kg/m^2)	0.05	0.33
Sex (Female)	0.08	0.29
HPV history (Yes)	0.04	0.41
Married Status (Married)	0.12	0.28
Comorbidity (Yes)	0.1	0.11

justified given the higher prevalence of symptoms and the more severe consequences of this virus in women than in men. Types 16 and 18 of this virus are associated with worse prognosis in women with cervical cancer, and therefore, women register higher requests for vaccination than men. Previous history of HPV infection was recorded in 12.7% of patients. Also, nearly 19% of patients had a history of concomitant underlying diseases. The incidence of complications was not significantly related to previous history, gender, age of patients, HPV infection, and underlying diseases.

The incidence of at least one complication immediately after vaccination, 7 days, 1 month, and 6 months after vaccination was estimated to be 26.5%, 9.8%, 7.2%, and 2.8%, respectively. In all four time periods, injection site pain was the most common complication of vaccination, accounting for more than 80% of complications in each period. The incidence of injection site pain immediately, 7 days, and 1 month after vaccination was 22.1%, 8.4%, and 5.7%, respectively. The incidence of complications decreased over time, which was justified given the nature of the adverse events that were reported acutely, as injection site pain decreased with time and the surrounding tissues regenerated.

In terms of severity of complications, the majority of complications were mild and improved with time and simple analgesics and cold compresses. Fever was reported only in the first few days after injection, and no cases of persistent fever were reported in subsequent periods. After pain at the injection site, gastrointestinal complications were common complications of vaccine administration. Severe and persistent complications were reported in only 4 participants, and these complications persisted for up to 6 months after injection. No serious or life-threatening complications requiring hospitalization were reported. The results of this study were consistent with the results of studies reported for other HPV vaccines [26, 30-35].

To our knowledge, the efficacy and short-term side effects of the papilloguard vaccine have only been evaluated in one controlled clinical trial compared to the Cervarix vaccine [26]. In this study, a randomized, controlled, double-blind, phase III trial by SM Afshani et al. [26] evaluated the safety of the bivalent papilloguard vaccine compared with Cervarix in 218 healthy female volunteers. It showed that the seroconversion rate of both vaccines was greater than 96%. Both vaccinated groups had a good overall profile of adverse events. Immediately after injection, 33% of patients had at least one transient adverse event. As in our study, the most common adverse event was pain at the injection site. In our study, the safety profile of Papilloguard was confirmed at mid-term follow-up in a suitable sample size of male and female participants. In our study, we did not evaluate vaccine efficacy.

Unlike papilloguard, the efficacy and safety of other 4- and 9-valent HPV vaccines, including 4- and 9-valent Gardasil, have been extensively evaluated at the community level. In a review of the safety and efficacy of HPV vaccines, focusing on Gardasil, Soliman et al. [30] demonstrated that Gardasil® HPV vaccines were safe and effective. They reported that Gardasil is largely considered safe for use. In another study, Luna et al. [32] evaluated the safety and efficacy of Gardasil™ in a long-term cohort study of adult women aged 24 to 45 years and reported no serious adverse events. Acute and transient adverse events, including injection site pain, were the most common adverse events following vaccination. Overall, they showed that vaccination with the qHPV vaccine

generally provided safe and effective protection against HPV-6, 11, 16, and 18-related genital warts and cervical dysplasia for up to 6 years after vaccination in women aged 24 to 45 years and was highly protective.

In a study by Vichnin et al. [33] Evaluating the safety of the quadrivalent human papillomavirus vaccine. They showed that the HPV-4 vaccine had a favorable safety profile. Key policy, medical, and regulatory organizations worldwide have independently reviewed these data and continue to recommend routine HPV vaccination, which is consistent with the results of our study. In another study, APF Costa et al. [34] confirmed the safety of the 9-valent HPV vaccine in a meta-analysis of three clinical trials. In a review, Phillips et al. [35] evaluated the safety of HPV vaccines and showed that all vaccines had acceptable safety profiles. Injection site reactions were slightly higher for the 9vHPV vaccine than for the 4vHPV vaccine. Overall, these vaccines had a very favorable safety profile, which confirmed the results of our study.

Strengths and Weaknesses

Our study had some weaknesses that should be noted. In this study, we used data recorded in the vaccine adverse event registration system for the Iranian population, so the results may not be generalizable to other populations. Also, in this study, participants were followed up by telephone, and adverse event registration was self-reported, which may have affected the results to some extent. A prospective study design with a long-term follow-up period can estimate the results more accurately. The most important strength of our study was the study of short- and medium-term adverse events of the Papilloguard vaccine in a large sample size.

In conclusions, our study showed that the incidence of short-term complications of the Papilloguard vaccine was low. Pain at the injection site was the most common complication of the vaccine, which was tolerable. The majority of complications were mild and transient. No serious complications requiring hospitalization were reported. Papilloguard vaccine was safe for injection, so it can be included in national vaccination guidelines to prevent HPV and its consequences.

Author Contribution Statement

Conceptualization: MKZ and ME; methodology: MKZ and ME; software: MKZ and ME; validation: MKZ and ME; Qualitative data collection and analysis: MKZ and ME ; investigation: MKZ and ME; resources, ME; data curation: MKZ and ME; writing—review and editing: MKZ and ME; supervision: MKZ; project administration. All authors have read and agreed to the published version of the manuscript.

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Not applicable.

Ethics approval

This study was approved by the Ethics Committee of the Iran University of Medical Sciences (Ethical code: IR.IUMS.FMD.REC.1403.140).

Availability of data

The datasets created and analyzed during this study are publicly available due to their availability. They can be obtained from the corresponding author upon request.

How the ethical issue was handled

Not required as data is not individualized, and primary data need to be collected.

Conflict of interest

None.

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