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Short Communication

Vaccination Program against HPV in Women with Excisional Treatment Due to Preneoplasic Cervical Lesions in the Region of Murcia: Results of the First Year

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Abstract

Introduction: Vaccination against HPV in women who underwent surgery due to high-grade CIN 2+ cervical lesions may reduce reinfection/reactivation. The Region of Murcia (Spain) launched a vaccination program of these women in April 2014. Our goal is to describe the demographic and health characteristics of the women included in the first 12 months of the program. 1.2. Material and methods: The women were derived to three regional centers for being vaccinated. A database collected compliance with the vaccine guidelines, prevalent HPV genotypes distribution, lesion causing the excisional procedure (conization) and age. A telephone survey on vaccine reactogenicity and tolerance was conducted.

Results: 200 women met the criteria to receive free immunization, 170 women, 85% (95% confidence interval 79.3, 89.6) completed immunization. The most frequently detected genotypes were 16 [63.5% of cases (95% confidence interval 54.6, 71.9)], 31 [13.9% (95% confidence interval 8.5, 21.1)] and 33 [7.7% (95% confidence interval 3.8, 13.8)]. 53% (95% confidence interval 46, 60) of women requiring cervical conization had CIN 3, 43% (95% confidence interval 36, 50) had CIN 2 and 4%(95% confidence interval 1, 7) had CIS. 65% (95% confidence interval 53, 75) of the women surveyed said not having suffered any adverse reaction; pain [21% (95% confidence interval 12, 31)] and inflammation [9.1% (95% confidence interval 3.7, 17.8)] were the most common adverse reactions. No woman required treatment from adverse reactions.

Discussion and conclusions: The implementation of the program is a successful strategy, with a 85% rate of posology compliance. We expect that the vaccine used will provide direct or cross-protection against the re-infection caused byhigh-risk vaccine and non-vaccine genotypes. The acceptability and vaccine safety was optimal.

ABBREVIATIONS

HPV: Human Papillomavirus; CIN: Cervical Intraepithelial Neoplasia; CIS: Carcinoma In-Situ; SD: Standard Deviation.

INTRODUCTION

Infections by the Human Papillomavirus (HPV) are associated with a significant burden of morbidity and mortality worldwide [1]. In Spain, 2511 cases or cervical cancer and 848 deaths are registered annually, thus being the second most common cancer in women aged 15 to 44 years [2] and the number of preneoplasic lesions (CIN 2+) is estimated between 25 000 and 47 000 [3].

Preventive measures against cervical cancer include screening, used in many Spanish Autonomous Communities opportunistically [4] (including the Autonomous Community of Murcia) as well as vaccination against HPV, introduced in our Region in 2008 for 14-year-old girls [5]. A positive test in

screening usually implies excisional treatment (conization) of high-grade lesions (CIN 2+) to prevent its progression to invasive carcinoma; however, after treatment reactivations/reinfections may appear in 5% to 30% of the cases, which requires careful monitoring and a second treatment after identifying the lesions [6].

It has been suggested that vaccine administration against HPV in women who had surgical treatment due to high-grade lesions (CIN 2-3) reduces the recurrence of those lesions in 64% to 88% of the cases in relation with unvaccinated women [6-8]. This fact led some international [9] and national guidelines [4] to recommend HPV vaccination to prevent subsequent disease after treatment. In this respect, the Autonomous Community of the Region of Murcia set up this procedure in April 2014 [10], being the first Spanish Region to implement this measure.

This study aims to describe social and health characteristics, compliance with vaccination guidelines, detected genotypes, type of lesion causing conization of cervix and vaccine tolerance for women included during the first 12 months of implementation of the program.

MATERIALS AND METHODS

The Region of Murcia is an Autonomous Community located in South-Eastern Spain with a population of nearly 1.5 million inhabitants. The program was implemented in April 2014. Previously, several meetings were held with the regional gynaecology teams and, after reaching a consensus on the contents of the program, these were made available to all public and private centres conducting excisional treatment.

Three centres in the Region were responsible for providing the vaccine against HPV included in the program (Cervarix). The target population were those women who were to undergo or had undergone a recent (<3 months) conization due to high-grade preneoplasic lesions.

The analysed variables were collected in a single regional database and included: compliance with posology, oncotypes detected using hybrid capture test (HPV HC2 testing (Digene Corporation,Silver Spring, MD)), lesion causing conization and age. Additionally, the women treated during the first 9 months were interviewed telephonically to ascertain vaccine reactogenicity and tolerance.

All data analysis was performed using IMB SSPSS Statistics for Windows, Version 22 (Armonk, NY: IBM Corp.). Qualitative variables were expressed as frequencies and percentages. For quantitative variables, the average and standard deviation (SD) were calculated. The comparisons of proportions were performed using a chi-square test ($\chi 2$) and the comparison of means was performed using One-Way ANOVA test. A significance level of 5% ($p \leq 0,05$) was considered in the statistical analysis.

RESULTS AND DISCUSSION

The results presented in this study reflect the data from the first Spanish vaccination program against HPV in women with excisional treatment due to preneoplasic lesions.

A total of 203 women requested the vaccine during the first year of implementation of the program (1 April 2014 to 31 March 2015); of these, 200 met the criteria for a free of charge administration of the vaccine against HPV and started vaccination (1st dose), 194 women received the second dose, 97% (95% confidence interval 93.6, 98.9) and 170 the third dose, 85% (95% confidence interval 79.3, 89.6). Among those who received the third dose, 167 women, [98.2% (95% confidence interval 94.9, 99.6)] complied with the intervals stated in the official prescribing information.

Determination of the genotype present in the lesion was available in 129 of the 203 women. Of them, genotype 16 was present in 82 cases [63.5% of the cases (95% confidence interval 54.6, 71.9)] either as a single genotype (n=67) or in a co-infection (n=15). The following most frequent genotypes were 31 in 18 cases [13.9% (95% confidence interval 8.5, 21.1)] and 33 in 10 cases [7.7%(95% confidence interval 3.8, 13.8)]. In 26of the 129women, genotypes appeared in co-infection (Figure 1).

The diagnosis that motivated surgical treatment was known in 193, of whom 53% (95% confidence interval 46, 60) (n=103) showed intraneoplasic lesion CIN 3, 43% (95% confidence interval 36, 50) (n=83) CIN 2 and 4% (95% confidence interval 1, 7) (n=7) carcinoma in-situ (CIS). All women with CIN2, CIN3 and CIS received the vaccine besides surgical treatment. The average age in the moment of the excisional procedure was 34.9 years and SD of 7.2. The average age of women with CIS was 39.8 years, 34 in the cases of CIN3 and 35.7 in the cases of CIN 2. The differences did not reach statistical significance.

Stratification according with the histological lesion shows that the frequency of genotype 16 increases as the lesion is more severe: 44.4% (95% confidence interval 30.9, 58.8) in CIN 2, 57.8% (95% confidence interval 44.8, 70.1) in CIN 3 and 66.7% (95% confidence interval 9.4, 99.2) in CIS; although the differences did not reach statistical significance (Table 1).

The first 77 women who joined the vaccination program were interviewed telephonically to ascertain vaccine reactogenicity/tolerance. 65% (95% confidence interval 53, 75) (n = 50) declared not having suffered any adverse effects. Between the adverse effects, pain was declared by 21% (95% confidence interval 12,

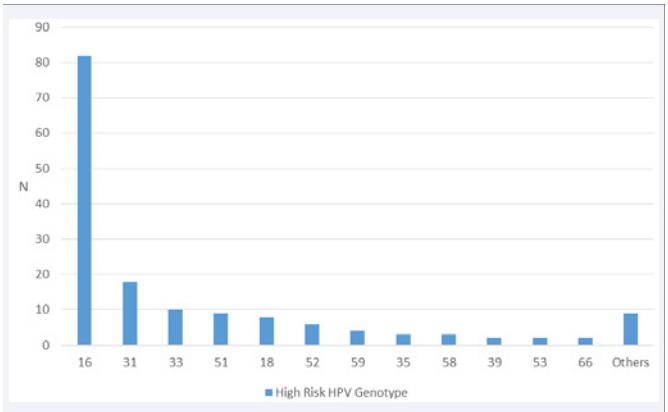

Figure 1 Absolute frequency of high risk HPV genotypes in women with high-grade cervical intraepithelial neoplasia from Region of Murcia (In 26 women, genotype appeared in co-infection).

Table 1: Distribution of subjects according to the HPV type infections stratified by histological diagnosis in Murcia.

Histological diagnosis	Causative genotype	N	Percentage	CI 95%
CIN 2	16	24	44.4	(30.9; 58.8)
	Co-infection (genotype 16 present)	6	11.1	(4.2; 22.6)
	Co-infection (genotype 16 absent)	6	11.1	(4.2; 22.6)
	Single HPV type (other)	18	33.3	(21.1; 47.5)
CIN 3	16	37	57.8	(44.8; 70.1)
	Co-infection (genotype 16 present)	8	12.5	(5.5; 23.1)
	Co-infection (genotype 16 absent)	5	7.81	(2.6; 17.3)
	Single HPV type (other)	14	21.9	(12.5; 34)
CIS	16	2	66.7	(9.4; 99.2)
	Single HPV type (other)	1	33.3	(0.84; 90.6)

Abbreviations: HPV: Human Papillomavirus; CIN: Cervical Intraepithelial Neoplasia; CIS: Carcinoma In-Situ; CI: Confidence Interval

31) (n=16) was predominant, together with inflammation 9.1% (95% confidence interval 3.7, 17.8), (n=7), tiredness-general malaise 3.9% (95% confidence interval 0.8, 11) (n=3) and fever 1.3% (95% confidence interval 0.03, 7.02) (n=1). None of the women required medication to treat adverse reactions.

Compliance with the posology of the vaccine in these women is high [85% (95% confidence interval 79.3, 89.6)] although somewhat lower that in the routine vaccination of adolescents in Spain (88.6%). Despite the high compliance, greater awareness allowing increasing coverage with the third dose would be necessary.

With respect to the genotypes present in the lesions, 16 [63.5%(95% confidence interval 54.6, 71.9)], 31 [13.9%(95% confidence interval 8.5, 21.1)] and 33 [7.7%(95% confidence interval 3.8, 13.8)] were the most common genotypes; our results resemble those obtained in a European study [11] in which genotypes 16, 31 and 33 were the most common in high-grade neoplasic lesions with 59.9, 10.5 and 9%, respectively, and somewhat higher that in the studies by Hartwig [3] in which genotypes 16 and 18 were present in 45.5% of CIN 2+ lesions and one American study [12] with genotypes 16 and 18 present between 53,6 and 57,1%. This genotype distribution in our Region allows us to be optimistic, since it is expected that the use prior to the beginning of sexual relations of both the bivalent vaccine (direct protection against genotype 16 and crossed-protection [13] against genotypes 31 and 33) and the new nonavalent vaccine (direct protection against all three genotypes) [14] will obtain a significant protection against the three most common genotypes in preneoplasic lesions in our Region.

Stratification by type of histological lesion shows a greater presence of genotype 16 in higher-grade lesions 44.4%(95% confidence interval 30.9, 58.8) in CIN 2 and 57.8%(95% confidence interval 44.8, 70.1)in CIN 3, similar results to those obtained in the aforementioned study [11] (42.5% in CIN 2 and 64.5% in CIN 3) and in the studies by Hartwig [3], Hariri [12] and Powell [15] in which genotypes 16 and 18 were present in 39% of CIN2 and 58% of CIN3; 53,6% of CIN2+ and 69,8% of CIN3/AIS and 56% of CIN2+ and 74,9% of CIN3/AIS, respectively. This data, although in our case does not reach statistical significance (probably due to the relatively small sample of our study), may indicate the higher oncogenicity of genotype 16 over all other genotypes isolated in our Region. The presence of genotype 16 increases when women who have a co-infection are included; thus, it would be present in 55.5% (95% confidence interval 41.4, 69.1) of women with CIN 2 and 70.3% (95% confidence interval 57.6, 81.1)of women with CIN 3.

The average age was 34.9, also similar to the aforementioned European study[11] in which average age at the time of diagnosis of high-grade lesions was 34, and 49 at the time of diagnosis of invasive cervical cancer.

CONCLUSION

Among the most encouraging data of this study is the small percentage of women who reported having suffered adverse effects, only 35%(95% confidence interval 24.5, 46.8), and the fact that none of them needed to take medication, which implies an excellent tolerance towards the vaccine; this data contrasts with that registered in pre-approval clinical trials [16] in which pain was observed in 78% of the cases (vs. 21% in our study), inflammation in 25.8% (vs. 9.1%) and tiredness-general malaise in 33% (vs. 3.9%) This difference can be explained by the population studied (higher average age in our study) and by the form of information collection, which might imply the existence of *a* memory bias in our study; however, we believe that the absence of need for treatment and the relatively high coverage of the third doses imply a high tolerance towards the vaccine in these patients.

Our study has several limitations. Firstly, we do not know the genotypes implied in the lesion in 74 of the 203 women participating; however, we do not believe that the distribution may be different in non-genotyped cases because the main reason to perform/not perform genotyping is merely administrative (availability of the technique depending of the health centre performing the conization). Secondly, we could not reach a causality attribution, especially in the cases presenting co-infection, because we have just one sample and not a serial determination that may allow us to attribute causality; however, the presence of genotypes 33 and 31 and especially 16 is so evident that it is of paramount importance to achieve protection against these genotypes in our Region. Thirdly, the small sample size may prevent us to reach statistical signification in some results, something we shall be able to achieve by including the patients during the second year of implementation of the program. Fourthly, we do not have exhaustive data on the reasons for non-compliance with the posology, although the data from

the telephone survey indicate that they may be related with administrative aspects and false perceptions about the safety of the vaccine [17]. This fact suggests the desirability of further investigation.

We believe that the implementation in Murcia of the vaccination program in women with excisional treatment has been a successful strategy with a high degree of compliance with the vaccination guidelines and good acceptability regarding the safety of the vaccine. It is expected the program may provide a significant clinical protection due to the genotypes identified. However, there is no complete agreement about the impact of the vaccination of women with excisional treatment,with favourable [6-8] and no favourable results [18]. Because of this, and as part of our vaccination program we plan to assess the effectiveness of the vaccine as a complementary therapy to excisional treatment due to preneoplasic lesions. Taking into account that since the beginning of the program most women are vaccinated,we plan to take historical controls (women with excisional treatment during 2012 and 2013) as no vaccinated and compare the recurrence of high-grade lesions in these women with the observed in women vaccinated from the outset of the program (April 2014- April 2016).

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