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Effectiveness of the human papillomavirus (types 6, 11, 16, and 18) vaccine in the treatment of children with recurrent respiratory papillomatosis

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ABSTRACT

Objective: To evaluate whether the quadrivalent human papillomavirus (HPV) (types 6, 11, 16, and 18) vaccine influences the clinical course of juvenile-onset recurrent respiratory papillomatosis (RRP) when administered to a group of patients with this condition.
Methods: Uncontrolled intervention study of patients with juvenile-onset RRP examined at the Pediatric Otorhinolaryngology Clinic, Federal University of São Paulo, where nine patients between the ages of nine and 17 received three doses of the prophylactic quadrivalent HPV vaccine (Gardasil®) and were followed for one year. Disease staging, intervals between relapses, intervals between surgeries, and the number of surgeries during the year prior to vaccination and during the first year after vaccination were compared.
Results: Eight patients were infected with HPV-6 and one with HPV-11. There were no statistically significant differences in the clinical scores ($p = 0.083$), anatomical scores ($p = 0.257$), intervals between relapses ($p = 0.062$), intervals between surgeries ($p = 0.357$), or the numbers of surgeries ($p = 0.180$) when the years before and after vaccination were compared. All patients had relapses following vaccination.
Conclusion: Patients with juvenile-onset RRP experienced a similar clinical course in the year after versus the year before vaccination with Gardasil®.

1. Introduction

Recurrent respiratory papillomatosis (RRP) is characterized by the proliferation of multiple papillomas in the respiratory tract that have a tendency to recur. RRP affects individuals of all ages and has varied clinical evolutions. Some patients require frequent interventions, whereas others can tolerate longer intervals between them. Depending on the age of onset of the symptoms, the disease is classified as juvenile-onset or adult-onset RRP. When the onset occurs in childhood, the patient tends to require a larger number of surgical procedures to control relapses.

RRP is caused by the human papillomavirus (HPV), most commonly types 6 and 11 [1]. It is believed that HPV is acquired during the perinatal period, during passage through the birth canal, or even by intrauterine transmission.

In general, recurrences persist until adulthood. However, in some cases, remission may occur spontaneously.

There is currently no cure for RRP, and surgery is the primary mode of treatment, which aims to maintain the patient's airways and improve their voice quality. However, even when all of the lesions have been resected, the disease tends to recur. Several adjuvants have been tested, but they have produced controversial results [1,2].

Recently, prophylactic HPV vaccines have been developed, consisting of protein L1 assembled into virus-like particles. Some authors have reported improvements in the clinical course of RRP after vaccination, suggesting that the vaccine can have therapeutic

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effects in addition to being a preventive [3–9]. In a dog with severe oral papillomatosis, administration of a canine oral papillomavirus L1 virus-like particle vaccine has also been reported, resulting in regression of the papillomas [10].

For RRP treatment, the primary focus of interest has been the quadrivalent HPV vaccine because it contains the virus types most often associated with the disease. In Brazil, the quadrivalent vaccine is marketed under the name Gardasil® and is recommended for boys and girls older than nine years of age.

The aim of this study was to assess whether the quadrivalent HPV vaccine (types 6, 11, 16, and 18) can influence the clinical course of juvenile-onset RRP when administered to patients with the condition.

2. Methods

Nine patients with juvenile-onset RRP examined at the Pediatric Otorhinolaryngology Clinic, Federal University of São Paulo (UNIFESP), were included in this study.

The following inclusion criteria were used:

1. patients with relapses after two or more surgeries for papilloma resection;
2. nine years of age or older;
3. under 18 years of age; and
4. disease confirmed histopathologically.

The following exclusion criteria were used:

1. chronic use of corticosteroids or immunosuppressants;
2. history of hypersensitivity to component(s) of the Gardasil® vaccine;
3. history of immunodeficiency;
4. patients undergoing radiation therapy and/or chemotherapy; and
5. current treatment with adjuvants.

For each patient, three doses of the Gardasil® vaccine (Merck Sharp & Dohme Corp., West Point, PA, EUA) were administered, as recommended by the manufacturer; the first dose was administered on the first day after papilloma resection surgery, the second dose was administered two months after the first dose, and the third dose was administered six months after the first dose. Histopathological examinations and viral typing were performed on resected papillomas.

Patients received medical consultations and nasofibrolaryngoscopic exams prior to vaccination and after three doses of the vaccine were administered.

For each patient, disease staging, intervals between relapses, intervals between surgeries, and the number of surgeries during the year prior to vaccination and during the first year after vaccination were compared. The year prior to vaccination was defined as the 12-month period prior to the first dose; the year after vaccination included the 12-month period that began 30 days after the third dose of Gardasil®.

To assess the severity of recurrences, the staging system proposed by Derkay et al. [11] was used. Based on this test, functional parameters and the extent of papillomatosis at different sites in the aerodigestive tract are numerically graded, generating a clinical score and an anatomical score. All staging was performed by the same evaluator.

Statistical analysis of all information collected in this study was initially done descriptively. The nonparametric paired Wilcoxon signed-rank test was used in order to compare the time periods before and after vaccination with respect to the anatomical and clinical scores, the intervals between relapses and surgery, as well as the total number of surgeries. For all conclusions based on inferential analysis, an alpha significance level of 5% was employed.

The study was approved by the University Ethics Committee (protocol number 1705/07) and written informed consent was obtained from patient's parent or legal guardian.

3. Results

Three patients in the sample were female and six were male. The mean age was 12.3 years, and the age range was nine to 17 years. The age of disease onset varied between one and eight years, and the mean age of onset was 4.4 years. Prior to participation in the study, the number of surgeries that patients had undergone ranged between two and 53 (Table 1).

During the study, the same surgical technique was used on all of the patients: papilloma resection with conventional cold microforceps by suspension laryngoscopy and visualization with an operating microscope. The surgical indications were dysphonia and dyspnea.

The resected lesions were sent for histological evaluation and to confirm the diagnosis of papilloma. No cases of dysplasia or malignancy were observed.

PCR analysis and sequencing were used to detect and identify the HPV type that caused the papilloma. Eight patients had HPV type 6, and only one patient had HPV type 11 (Table 1).

All patients received three doses of Gardasil® postoperatively. The first dose was administered on the day following a surgical procedure. None of the patients experienced adverse reactions to the vaccine.

An important objective of this investigation was the comparison of two different time periods: the year prior to HPV vaccination (pre-vaccination) and the first year after vaccination (post-vaccination). Clinical and anatomical scores, intervals between relapses and surgeries, and the total number of surgeries were compared. The clinical score during the pre-vaccination period ranged from two to three, whereas it varied from one to three during the post-vaccination period. The anatomical scores ranged from two to 13 during the pre-vaccination period, whereas they ranged from two to 14 during the post-vaccination period. The mean interval between relapses during the pre-vaccination period was 4.1 months, with a range of one to 10 months, and during the post-vaccination period, the average interval between relapses was six months and ranged from one to 12 months. During the pre-vaccination period the average interval between surgeries was 8.6 months, ranging from five to 12 months. During the post-vaccination period, the mean interval between surgeries was 9.0 months, ranging from three to 12 months. During the pre-vaccination period, between zero and two surgeries were performed. During the post-vaccination period, the number of

Table 1
Patient characteristics.

Patient	Age (years)	Gender	Age at disease onset (years)	Number of previous surgeries	HPV type
1	11	F	5	7	6
2	17	M	2	20	6
3	14	F	6	8	6
4	9	M	6	2	6
5	14	M	8	4	6
6	11	F	1	21	6
7	9	M	1	53	11
8	11	M	8	2	6
9	15	M	3	13	6