Effectiveness of Varicella Vaccines as Postexposure Prophylaxis

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Background: Although chickenpox is usually a mild disease, it is not always free of complications, especially in adolescents and adults. Previous studies of postexposure prophylaxis conducted with experimental vaccines showed the vaccine to be highly effective if administered in the first 3 to 5 days after exposure. However, studies carried out with commercialized vaccines yielded discordant results. The aim of the present study was to assess the effectiveness of currently available varicella vaccines as postexposure prophylaxis.

Methods: We conducted a prospective cohort study. Patients susceptible to chickenpox consulting at the Preventive Medicine Department of the Vall d'Hebron Hospital after household exposure to a case of chickenpox were included. Postexposure prophylaxis with varicella vaccine was administered within the first 5 days after contact. Subjects were interviewed by telephone between 4 and 8 weeks after vaccination to ascertain whether chickenpox had appeared and, if so, its severity. The effectiveness of the vaccine in preventing and attenuating the disease was calculated with a confidence interval of 95%.

Results: Sixty-seven subjects were included in the study. Effectiveness of the varicella vaccine in preventing any type of disease was 62.3% (CI 95%: 47.8–74.9) and 79.4% (CI 95%: 66.4–88.9) in preventing moderate and severe disease. No statistically significant differences were found when effectiveness was compared according to sex, age, or days elapsed since exposure.

Conclusions: Administration of varicella vaccines within the first 5 days postexposure is effective in preventing chickenpox and in attenuating the illness.

Key Words: chickenpox, varicella vaccine, effectiveness, postexposure prophylaxis, prevention

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Chickenpox currently constitutes the most frequent exanthematous disease in countries where vaccination has not yet been included in routine immunizations. Although chickenpox is usually a mild and self-limited disease, severe complications may occur. These are seen more frequently in immunocompromized patients, those with lung or chronic skin diseases, pregnant women, children less than 1 year of age, adolescents and adults. Chickenpox-related mortality and morbidity are higher in adults, with a risk of complications 10 to 20 times higher than in children. The main complication is pneumonia which appears in 1 of 400 healthy adults who contract chickenpox.[1,2] In the prevaccine era in the United States, the average case-fatality for varicella ranged from 2.0 to 3.6 per 100,000 cases, with higher rates among infants and adults. Between 1990 and 1994, the risk of varicella-related death was 25 times higher in adults than in children 1 to 4 years old.[3]

In Spain, the annual incidence of complications requiring hospitalization is 2.7 cases/100,000 individuals, with death occurring in 3 to 6 cases per year.[4,5] The incidence of chickenpox is higher in preschool children and in those in the first years at school, although a small number of infections occur between the ages of 15 and 34 years, when the risk of complications is greater.[6,7]

The use of the varicella vaccine in postexposure prophylaxis was recommended in 1999 by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention and by the American Academy of Pediatrics, based on previous studies suggesting the vaccine was effective if administered within the first 3 days after exposure and up to a maximum of 5 days.[8,9] This recommendation is based on the fact that vaccines derived from the Oka strain induce an immune response in 5 to 7 days and the incubation period of varicella is 10 to 21 days.[10] However, these recommendations are mainly based on studies conducted with experimental vaccines, whose formulations and compositions differ from those of currently available vaccines[11–13]; only one of the studies used a licensed vaccine.[14] Later published articles which analyzed the effectiveness of the currently used vaccines showed discordant results, probably because of methodologic differences, the inclusion of nonhomogeneous populations, and insufficient sample sizes.[15–17]

The aim of the present study was to evaluate the effectiveness of the currently available varicella vaccines for postexposure prophylaxis in our setting.

MATERIALS AND METHODS

Design

We conducted a prospective cohort study design with historic controls as a comparison group.

Study Population

We enrolled individuals attending the Preventive Medicine and Epidemiology Department of Vall d'Hebron Hospital (Barcelona, Spain) after household exposure to a case of chickenpox if they met the following inclusion criteria:

1. Subjects greater than 1 year of age exposed in a household setting to a chickenpox primary case for a minimum of 5 minutes of indoor and face-to-face contact.[18] Primary cases were considered only if they were the first case in a household (no cases occurring 3–4 weeks prior to this case).
2. Susceptibility to chickenpox. Susceptibility was defined as a negative history of the disease and no evidence of previous vaccination. We performed rapid (<12 hours) serologic confirmation of susceptibility in persons 13 years of age and older. Antivaricella-zoster IgG antibodies were determined using the fluorimetric enzymoimmunoanalysis technique (Vidas; bioMérieux).
3. Varicella vaccine administration within the first 5 days after exposure.

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Study Period

The study was conducted from May 2002 to May 2007.

Variables

We collected the following information: age (classified in 2 groups: under 13 and 13 or over), sex, history of varicella, number of days since exposure and comorbidity (immune deficiency, pregnancy, corticoid treatment, or other immunosuppressive therapy).

Rash presentation in the primary case was considered as the onset time of exposure.

We collected data using a standardized questionnaire.

Postexposure Prophylaxis

Vaccines used as postexposure prophylaxis were Varilrix (GSK), which contains a minimum of 1995 plaque-forming units of the dose-attenuated Oka strain virus, or Varivax (Sanofi Pasteur MSD), which contains a minimum of 1350 plaque-forming units of dose-attenuated virus. Both vaccines were administered in a nonrandom fashion subcutaneously in the deltoid muscle. Subjects less than 13 years old received a single dose and subjects 13 years and older received 2 doses, 1 month apart.

Outcome

Subjects were telephoned 4 to 8 weeks after vaccination to determine whether they had developed chickenpox. Secondary cases were defined as those who developed varicella 10 to 21 days after rash onset in the primary case, thereby excluding coprimary cases and cases who developed chickenpox more than 21 days after exposure. Diagnosis of the disease was based on the description of the rash provided by the patients. Information on the number of skin lesions and the need for hospitalization was collected to determine the severity of infection. Chickenpox was classified as mild if fewer than 50 lesions were present, moderate if 50 to 500 were present, and severe in case of more than 500 lesions or hospitalization due to chickenpox complications.[17]

Epidemiologic and Statistical Analysis

Data were described using frequencies and corresponding percentages for qualitative variables and by means with standard deviation (SD) or medians with interquartile range (IQR) for continuous variables.

Vaccine effectiveness as postexposure prophylaxis was calculated using the formula of vaccine effectiveness in cohort studies[19]:

$$VE = 1 - (AR_V/AR_N) \times 100$$

where VE indicates vaccine effectiveness; AR_V, Attack rate in vaccinated; AR_N, Attack rate in nonvaccinated.

Vaccine effectiveness in preventing moderate and severe disease was calculated by the same formula, with those who developed mild chickenpox being considered as noncases.

An historic secondary attack rate of 87% among susceptible household contacts was used as the attack rate in the nonvaccinated population for both vaccine effectiveness calculations.[20]

The χ^2 test or Fisher exact test were used to measure the association between chickenpox development and sex, age, and time elapsed since exposure. P values <0.05 were considered statistically significant.

Data were analyzed using SPSS version 13.0[21] and Stata version 8.2.[22]

RESULTS

During the study period, 67 subjects met the inclusion criteria and had outcome results. Twenty-one of the subjects were less than 13 years old. Median age for children was 2 years (IQR = 6) and for adolescents and adults it was 34 years (IQR = 9). Women represented 43% of the population. Varilrix was used in 55 cases and Varivax in 12 cases. Seventy-three percent of the subjects were vaccinated within 72 hours postexposure and 27% between the fourth and fifth days. Mean time from exposure to vaccination was 2.72 days (SD: 0.14) and median time was 3 days. None of the primary cases was previously vaccinated with varicella vaccine.

TABLE 1. Distribution of Variables According to Chickenpox Development

Variable	No Varicella n (%)	Varicella n (%)	Attack Rate (%)	*P*
Sex				0.44
Female	21 (72.4)	8 (27.6)	27.6	
Male	24 (63.2)	14 (36.8)	36.8	
Age				0.27
Under 13 yr	12 (57.1)	9 (42.9)	42.9	
13 yr or over	33 (71.7)	13 (28.3)	28.3	
Number of days since contact				0.77
≤3 d	32 (65.3)	17 (34.7)	34.7	
4–5 d	13 (72.2)	5 (27.8)	27.8	
Total	45 (67.2)	22 (32.8)	32.8	

Comparative analysis using the χ^2 test.
P: *P* value.

Forty-five contacts did not develop varicella (67%), 10 developed mild chickenpox (15%), and 12 moderate chickenpox (18%). No patient developed severe disease.

Vaccine effectiveness in preventing all forms of varicella was 62.3% (CI 95%: 47.8–74.9) and effectiveness in preventing moderate and severe disease was 79.4% (CI 95%: 66.4–88.9). No statistically significant differences were found in the chickenpox attack rate according to sex, age, or days elapsed since exposure (Table 1).

DISCUSSION

The effectiveness calculated in our study lies within the range of values described by other authors (Table 2).[11–17,23–25]

The first studies to demonstrate the effectiveness of the varicella vaccine in postexposure prophylaxis were conducted in Japan in the 1970s using experimental vaccines.[12,13] Later studies in the 1980s confirmed high effectiveness of the vaccine when administered within the first 3 days postexposure.[11,23–25] However, the manufacturing process for vaccines has changed and currently used products have a different formulation and lower antigenic content.

A few observational studies have assessed the effectiveness of currently available vaccines in postexposure prophylaxis with discordant results.[14,15,17] Mor et al performed the only randomized, double-blind, placebo-controlled clinical trial to date to evaluate the effectiveness of a licensed vaccine (Varilrix).[16,26] The studies conducted to date show contradictory results, rendering their comparison difficult. There were methodologic differences among studies, sample sizes were small and most of the experimental vaccines used in the first studies (which had better results) had a greater antigenic load (Table 2).

Factors such as age and time elapsed between exposure and vaccination must be considered. The influence of age on vaccine effectiveness is well described in preexposure prophylaxis.[27,28] All but one of the published studies[15] on postexposure prophylaxis were conducted in children. Our study included both children and adults, permitting investigation of age; however, no statistically

TABLE 2. Main Published Studies on the Efficacy/Effectiveness of Chickenpox Vaccine in Postexposure Prophylaxis

Author/yr	Study Design	Antigenic Load of the Vaccine (PFUs)	Subjects (n)	Type of Contact	Study Population	Days Elapsed Since Contact	Efficacy/Effectiveness to Prevent Varicella (%)	Efficacy/Effectiveness to Attenuate Varicella (%)
Takahashi/1974[13]	Prospective observational	Experimental vaccine	23	Hospital	Children 6 mo–12 yr	0	100	—
Asano/1977[12]	Controlled clinical trial	800–1000 Oka/Biken	37	Household	Children 1 mo–11 yr	3	100	—
Asano/1982[23]	Prospective observational	800–15000 Oka/Biken	30	Household	Children 6 mo–7 yr	3	100	—
Katsushima/1984[24]	Several prospective observational (n = 17)	250–3000 Oka/Biken	163	Hospital	Children	1–5	*100*	—
Naganuma/1984[25]	Prospective observational	300–2000 Oka/Biken	46 40	Hospital Household	Children	—	*80*	—
Arbeter/1986[11]	Double-blinded, placebo controlled randomized trial	4350 Oka/Merck	26	Household	Children 18 mo–16 yr	<3 5	90 67	100
Salzman/1998[14]	Prospective cohort study with historic control group	>1350 OkaMerck Varivax	10	Household	Children 14 mo–12 yr	3	*42.5*	*88.5*
Watson/2000[17]	Prospective cohort study with historic control group	>1350 OkaMerck Varivax	42	Homeless shelter	Children 12 mo–12 yr	1.5	94.5	100
Gentile/2002[15]	Prospective cohort study with historic control group	>1995 Oka GSK Varilrix	104	Household (91.3%) and school	Children >12 mo and adults	<2 5	87.5 83.7	—
Mor/2004[16]	Double-blinded, placebo controlled randomized trial	>1995 Oka GSK Varilrix	42	Household	Children 12 mo–13 yr	3	*9.1*	*87.5*

Data in italics were not contributed by the authors of the study, but calculated using information from the authors. An attack rate of 87% was used for the nonvaccinated population.

significant differences were observed. Our study included only secondary cases that had developed varicella from 10 to 21 days after exposure and for this reason adults who developed varicella received only 1 dose of vaccine, not the recommended 2-doses with a 1-month interval.

Attack rates in subjects less than 13 years old were higher than in contacts over 13 years old, although the difference was not statistically significant. Even though all adults were serologically tested, some could have been false negatives owing to a lack of test sensitivity.

The mean time from exposure to vaccination in our study was 2.7 days, slightly higher than reported in other works, such as that of Mor et al, whose mean time was 1.9 days.[16] Previous studies detected a relationship between vaccine effectiveness and time elapsed since exposure, with better results with vaccination in the first 72 hours than after the fourth day (90% vs 67%, respectively).[11] Our study found only a 7% difference between both attack rates, which would support the clinical practice of postexposure vaccination if time elapsed since exposure is 5 days or less.

Study limitations should also be considered. First, diagnosis of chickenpox in contacts was based on the information provided by telephone and not by a physician examination. Chickenpox is an easily identifiable disease which was previously observed in the index case by the majority of contacts. Nonetheless, vaccination could modify the disease and reduce the detection of mild clinical presentations, thus overestimating vaccine effectiveness.

Second, children with a negative history of varicella were assumed to be susceptible. We consider this a minor limitation since previous studies demonstrated that the reliability of a negative history is more accurate in young children[29,30] and the median age of children in our study was 2 years. One study showed that seroprevalence of varicella among children with a negative history of varicella ranged from 9% in 7- year-olds to 13% in 12-years-olds.[30] Considering this result and the age distribution in our study, 2 children could have been misclassified as susceptible and vaccine effectiveness therefore overestimated.

Third, the possibility that postvaccination rash was considered vaccine failure cannot be ruled out. The risk of varicella-like reactions associated with the vaccine ranged from 3% to 5%.[9,31] However, molecular biology techniques are often required to distinguish between infections by wild and vaccine viruses. A possible classification bias may have occurred and could have led to vaccine effectiveness being underestimated.

It is obvious that the best epidemiologic design to evaluate our hypothesis would be a clinical trial. However, as the recommendations for postexposure prophylaxis in Catalonia are well defined,[32] it would not be justifiable on ethical grounds to use an experimental approach.

Finally, the chickenpox attack rate for any form of varicella in nonvaccinated subjects was used to calculate vaccine effectiveness in attenuating disease progression, thereby overestimating effectiveness.

In conclusion, available varicella vaccines administered within 5 days after exposure to chickenpox are effective in preventing chickenpox and highly effective in attenuating the disease.

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