Trans. Nat. Acad. Science & Tech. (Phils.)
1988: 10: 437-446

CLINICAL OBSERVATIONS ON THE FIRST VARICELLA VACCINEES IN THE PHILIPPINES WITH LIVE ATTENUATED OKA STRAIN VACCINE (1987)

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ABSTRACT

This study reports on a group of 50 healthy children, with ages 1 to 19 years, the first to be vaccinated with live attenuated varicella vaccine with Oka strain by M. Takahashi in the Philippines. Skin tests were available for 25 children before and after vaccination. The pre-test serves to exclude those already immune while the post-test serves to determine response to vaccination. The study also presents immediate local (pain, redness, swelling) and systemic reactions (fever, rash, malaise, vomiting, convulsion or any acute manifestations). Those who were exposed to varicella after vaccinations were observed for protection against the disease.

Introduction

Varicella (chickenpox) is an acute highly contagious common childhood disease caused by herpes virus varicellas or varicella-zoster virus (VZV). It may not appear as an alarming illness as it is not among the first ten causes of morbidity or mortality in health statistics of either children or adults. It has, however, been manifested in occasional epidemics in crowded houses and localities, and in institutions for children like orphanages, vacation camps and schools.

On the whole, the manifestations are not severe, particularly in the younger age groups. Children may have to stay away from school for more than a week. Among adolescents and adults, the disease may be severe as well as in neonates infected in utero. Among complications are secondary skin infections like furuncles and erysipelas. Occasionally penumonitis, encephalitis and Reyes' syndrome have been reported in varicella. High mortality has been observed in patients with compromised immunosuppressive therapy, in neonates, and during pregnancy.

While immunizations against most childhood exanthematas like variola (smallpox), rubella (German measles) and rubeola (measles) have already been developed, accepted and used routinely, it was not until 1970 that the vaccine against varicella was studied and successfully developed by Takahashi of Japan in 1974. In the case of variola it is well-known that the disease has already been successfully controlled and eradicated. A major and significant factor in this achievement has been smallpox vaccination.

Clinical trials of varicella vaccine have been carried out, first in Japan where a group of 70 healthy children were the first vaccinees (1974). Their number has reached over 4,500 in that country. The results have been favorable and convincing.

In 1987 *50 doses of the Oka strain of varicella vaccine was made available to the Children's Medical Center Philippines. The present paper is limited only to clinical observations from July 1987 to February 1988, due to lack of facilities to do varicella viral or serological examinations. As there will be forthcoming opportunities to increase the number of vaccinees, the authors present this paper for guidance and reference in subsequent studies.

Clinical trials were also performed in 137 healthy children (Weibel *et al.*, 1983), though the vaccine was first used in 1981 among 1,200 healthy children also in the USA. Other studies conducted in Europe have equally been favorable. These studies confirm the safety and immunogenecity of live attenuated varicella virus in healthy children.

Evidently, the vaccine may soon be considered an additional acceptable procedure in the field of immunization. Its successful use has even been extended to children with chronic diseases.

Objectives

The Oka-Biken strain of varicella vaccine was used for clinical trial involving 50 health children in Metro Manila with the following objectives:

1. To evaluate clinical reactions of the vaccine within a few days or a months after vaccination;
2. To observe later reactions 5-8 months after;
3. To observe occurrence of varicella among those who have been exposed to the disease after vaccination, particularly to household or family contacts;
4. To try the use of varicella skin test pre- and post-vaccination with the limited number of seventy of tests that were available in this study; and
5. To serve as initial guidelines and reference for subsequent studies.

Materials and Methods

The vaccine

Oka-Biken Varicella Zoster Virus (VZV) vaccine was used in this study. This strain was originally isolated from a child named Oka who had varicella and was

*After the date of reporting this study, 40 doses of this vaccine became available to the authors from the same source.

developed by M. Takahashi and colleagues in 1974 at Biken Institute in Osaka, Japan – hence the name Oka-Biken vaccine. This vaccine is a product of purified live, attenuated varicella virus cultivated in human diploied cells. It is dissolved in 0.7 mL of distilled water, and is 0.5 mL dose subcutaneous injection in the deltoid region. This dose gives an infecting unit of more than 1000 plaque forming units (PFU).

VZV skin test antigen

A limited amount of soluble VZV antigen for skin testing prepared by Asano, Shiraki, Takahashi (1981) from fluid of infected cultures was made available for the study. The antigen is injected intradermally (0.1 mL) in the forearm and the reaction is measured after 48 hours as millimeters of erythema. A reaction is considered positive with an erythema of five mm or more. In the present study, post-vaccination skin testing was done two weeks after vaccination.

Study subjects

Fifty healthy children of both sexes aged 1 year to 19 years participated in this study. They were chosen from private pediatric outpatients. Written consent was obtained from the child's parent or guardian prior to immunization. No one had previous clinical history of varicella. The following contraindications were observed:

1. Fever and deficiency in nutrition as noted clinically;
2. Disease of heart, kidney and liver (except for one who had congenital heart disease);
3. Kanamycin and erythromycin sensitivity;
4. Convulsions within at least 12 months; and
5. Those within 1 month after vaccination of polio, measles, rubella, mumps and BCG.

The subjects were asked to fill up forms initially, agree to follow-ups and report in case of untoward manifestations or doubtful developments after vaccination.

Clinical follow-up

The subjects were advised to come back two weeks after vaccination to record reactions in the injection site and to determine fever, rash or other pertinent manifestations. For some who had initial skin testing, a post-vaccination test was done.

Subsequent follow-ups through personal interview or by telephone was done 5-8 months later to determine immediate and late reactions, exposure to natural varicella and development of disease in order to update the initial questionnaire. A follow-up medical examination of each vaccinee was done by one of the authors in February 1988 or seven months after vaccinations. This occasion gave the

authors an opportunity to update each vaccinee's date with a review of health records and the confirming of any unnoticed or disregarded details in the parents' observations.

Observations

Fifty children were vaccinated with VZV vaccine, Oka-Biken strain from July to October 1987. Of the study group, 36% were males and 64% females. The mean age of the children was 5.75 years. Table 1 shows the age-sex distribution of the vaccinees.

Table 1. Age-sex distribution of vaccinees

Age (Years)	*Male*	*Female*
1-4	6	18
5-9	9	10
10-14	2	2
15-19	1	2
Total (%)	18 (36%)	32 (64%)

The children were apparently well at the time of vaccination with weight percentile ranging from 3% to 97%.

Of the 50 vaccinees, 48 were subjected to follow-ups. Excluded was one whose location could not be ascertained and another who was exposed to household contacts three weeks prior to vaccination and manifested the disease four days post-vaccination. The immediate post-vaccination clinical reactions are enumerated in Table 2.

Reactions in each vaccinee were, at times, multiple. Thus, two subjects had both pain and redness while one had redness swelling and fever during the first 48 hours. These reactions may therefore be recorded more than once and thus result in figures higher than the number of vaccinees.

Fever in 23% of vaccinees lasted approximately 1-3 days with six of 48 (12.5%) occurring for only one day. Six of 48 febrile reactions (12.5%) occurred in the first week, four of 48 (8.3%) in the second week and one in 48 (2.1%) in the third week, respectively.

Four percent of the rashes appeared two weeks after vaccination and were seen by doctors. One was diagnosed as insect bites and another as varicella.

Of the 50 vaccinees, 25 had pre-and post-vaccination skin tests; 20 had pre-vaccination skin test only and five had neither. All the pre-vaccination skin tests gave negative results. Post-vaccination skin test results of 25 vaccinees observed two weeks later are shown in Table 3.

Table 2. Post-vaccination clinical reactions

Reaction	*Number*	*Percentage*
1. Injection site		
Pain	8	17
Redness	9	19
Swelling	1	2
2. Fever	11	23
3. Rashes		
Frickly heat-like	1	2
Insect bite-Appearance	2	4

Table 3. Post-vaccination skin test of 25 vaccinees

Reaction	*Number*	*Percentage*
Less than 5 mm	11	44%
5 mm or more	14	56%

Three of the subjects had exposure to varicella prior to vaccination while two potential vaccinees upon screening, had exposure. Clinical data of these five exposed children are presented in Table 4.

On further follow-up, eight vaccinees were exposed to varicella, one having been exposed twice. Table 5 shows their clinical data.

Discussion

During the first 38 hours after injection, 31% of vaccinated children reported pain, redness and swelling at the injection sites though these readily subsided. The results are comparable with those reported by Weibel *et al.*, in 1984 using Oka-Merck vaccine which included 27% of vaccinated children and 19% of controls. He noted pain and redness as significantly more common among vaccinees than among placebo recipients. In the present study, pain and redness are recorded as 17% and 19%, respectively. No reaction was noted after the second day while there were a few local reactions reported after the third day.

As regards fever, the febrile episodes of 23% of the subjects was higher than the summarized report of 12% by Arbeter *et al* using Oka-Biken strain (1984). However, five had other symptoms like cough, cold, headache and myalgia, a total of 10% which could be attributed to concurrent non-varicella infections. The febrile

Table 4. Clinical data of five subjects who had previous exposure to varicella

Subject	*Age*	*Exposure*	*Type of*	*Pre-Vacc.*	*Vacc.*	*Clinical*
Code No.	*(Years)*	*Interval*	*Exposure*	*Skin Test*	*Date*	*Varicella*
8	5	3 weeks	Household	Negative	7/13/87	Yes (4 days post-vacc.)
19	17	3 weeks	Households	Negative	7/20/87	No
54	4	2 months	Households	Negative	9/11/87	No
44	1	4 months	Neighborhood	Positive	not done	No
55	8	1 month	Neighborhood	Positive	not done	No (had further exposure 4 months later)

Table 5. Clinical data of nine subjects who were exposed after vaccination

Subject	*Age*	*Pre. Vacc.*	*Vacc.*	*Post-Vacc.*	*Interval*	*Where*	*Clinical*
Code No.	*(Years)*	*Skin Test*	*Date*	*Skin Test*	*Bet. Vacc. & Exposure*	*Exposed*	*Varicella*
10	5	negative	7/18/87	not done	1 month	school	No
11	2	negative	7/18/87	5 mm	6 months	Household	No
31	9	negative	8/17/87	not done	3 months	school	No
32	2	negative	8/17/87	not done	4 months	neighborhood	No
33	3	negative	8/15/87	not done	3 months	neighborhood	No
51	8	not done	9/5/87	not done	1 week	school	No
					5 months	neighborhood	No
52	5	not done	9/5/87	not done	5 months	neighborhood	No
53	7	not done	9/13/87	not done	1 week	school	No

better measured by exposure to a natural varicella and non-development of disease. Results of a long term follow-up study indicate that the vaccine-induced protective immunity persists for approximately one decade in 95% and is almost equal to the long-term immunity following natural infection (Asano *et al.*, 1985).

Summary and Conclusions

In 1987 the Children's Medical Center Philippines (CMCP) obtained 50 doses of live attenuated varicella virus vaccine, Oka-Biken strain, from the University of Osaka, Japan, Department of Virology through its Head, M. Takahashi. Together with the vaccine was a limited amount of skin test antigen.

Fifty (50) healthy children, 1 to 19 years old from Metro Manila were the participants in this study. As advised by Takahashi, certain criteria were followed in the choice of the vaccinees and these were from the Outpatient Department of CMCP.

With signed consents from parents and an agreement to return for follow-ups as advised, vaccination was started in July 1987. Through personal interviews, questionnaires and follow-up visits conducted as needed, which included a medical examination in February 1988, the study was done within a period of eight months. Only one was lost to follow-up and one developed varicella 4 days after vaccination due to a previous exposure. Thus this study includes observations only on a total of 48 vaccinees.

The vaccine was injected subcutaneously in the deltoid region and the next personal follow-up was done two weeks later. Skin tests were available only to 25 vaccinees who had both pre- and post-testings, 20 had only pre-vaccination tests and five had neither. Readings were done 48 hours after testing and a positive test was an erythema of 5 mm or more.

The main clinical reactions observed were pain (17%), redness (19%), fever (10.4%), and rashes (4%) which were readily relieved.

In general the above reactions were well-tolerated and mild, causing no alarm to the parents. Vaccine reactivation as *zoster* had not occurred in the studies abroad nor in this limited study.

Pre-vaccination tests results in all 45 vaccinees were negative. Post-vaccination skin tests after two weeks (the duration recommended) gave positive results in 56%. Abroad, serial testings were done in their study subjects together with serological tests. In the present study such serial testing was not possible due to limited antigen.

Within the 8-month period of observation no vaccinee contracted varicella even if eight were exposed to the disease after vaccination.

With the limited study in 48 vaccinees and a brief observation period of 8 months, the authors initially conclude, just like Takahashi's initial study on 70 healthy children and in 80 of the first healthy vaccinees of A. Arbeter *et al*, that the vaccine is safe and effective. Undoubtedly, a similar study with more subjects

and requiring a longer observation period may be necessary to establish or confirm the conclusiveness of this study.

Acknowledgment

The authors acknowledge with gratitude and appreciation the kindness and generosity of Michiaki Takahashi, MD, Chairman of the Virology Department of the Research Institute for Microbial Diseases, Osaka University, Japan, for accomodating a request for the varicella vaccine and skin test antigen and which made this study possible. His guidance and help through personal communications and reprints of his studies, clinical trials, laboratory researches and experiences, have been most helpful. For all these, the authors cannot thank him enough and adequately.

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