# Antibody response of patients after postexposure rabies vaccination with small intradermal doses of purified chick embryo cell vaccine or purified Vero cell rabies vaccine

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Although the introduction of tissue culture vaccines for rabies has dramatically improved the immunogenicity and safety of rabies vaccines, they are often prohibitively expensive for developing countries. To examine whether smaller doses of these vaccines could be used, we tested the safety and immunogenicity of purified chick embryo cell vaccine (PCECV) on 211 patients in Thailand with World Health Organization (WHO) category II and III exposures to rabies. The patients presented at two Thai hospitals and were randomized into three groups. Patients in Group 1 received 0.1 ml PCECV intradermally at two sites on days 0, 3, 7, and at one site on days 30 and 90. Group 2 was treated similarly, except that purified Vero cell rabies vaccine (PVRV) was used instead of PCECV. Group 3 received 1.0 ml PCECV intramuscularly on days 0, 3, 7, 14, 30 and 90. After 0, 3, 7, 14, 30 and 90 days serum was collected from the subjects and the geometric mean titres (GMTs) of rabies virus neutralizing antibody determined. After 14 days the GMT of 59 patients vaccinated intradermally with PCECV was equivalent to that of patients who received PVRV. Adverse reactions were more frequent in patients who received vaccines intradermally, indicating the reactions were associated with the route of injection, rather than the vaccine *per se*. We conclude that PCECV is a safe and highly immunogenic vaccine for postexposure rabies vaccination when administered intradermally in 0.1-ml doses using the two-site method (''2,2,2,0,1,1'') recommended by WHO.

**Keywords:** rabies vaccine, administration and dosage, adverse effects; chick embryo; Vero cells, immunology; antibody formation; comparative study; Thailand.

*Voir page 697 le résumé en français. En la página 697 figura un resumen en español.*

## Introduction

Rabies is considered to be a fatal disease once clinical symptoms develop in humans and animals. Although the introduction of tissue culture vaccines has dramatically improved the immunogenicity and safety of rabies vaccines, these vaccines are often expensive in developing countries and not affordable by most of the individuals at highest risk of exposure. To reduce the cost of tissue culture vaccines for postexposure treatment alternate vaccination protocols have been developed that require less vaccine, including several that rely on intradermal administration to reduce the quantity of vaccine needed to elicit a satisfactory immune response.

In 1992, the World Health Organization (WHO) recommended that the two-site intradermal method could be used for postexposure treatment (*1*). By this method, two doses of vaccine are administered at two sites intradermally on days 0, 3, and 7, no dose is administered on day 14, and one dose of vaccine is administered at a single site on days 30 and 90 ("2,2,2,0,1,1"). In 1997, based on the results of an earlier study (*2*), the WHO Expert Committee on Rabies also recommended that each intradermal dose should be one-fifth the volume of vaccine required for intramuscular administration (*3*). For purified chick embryo cell vaccine (PCECV) and purified Vero cell rabies vaccine (PVRV) the recommended intramuscular doses are 1.0 ml and 0.5 ml, respectively, indicating that the appropriate intradermal doses would be 0.2 ml for PCECV and 0.1 ml for PVRV.

Previous studies have reported that intradermal doses of PCECV even as low as 0.1 ml could induce a satisfactory antibody response (*4–6*). However, these were simulated postexposure stu-

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dies, conducted in clinically healthy individuals and not in patients that were exposed to rabies. Nevertheless, if the amount of PCECV required to induce an immune response could be reduced by one-half, from 0.2 ml to 0.1 ml, twice as many patients in developing countries could be treated. To determine if the recommended volume of PCECV for intradermal postexposure treatment could be safely reduced to 0.1 ml per site, from 0.2 ml per site, we designed a comparative study between PVRV and PCECV using the two-site method in patients with category II and III rabies exposures.

## Materials and methods

### Vaccines and immunoglobulin

Commercial lots of two tissue culture human rabies vaccine were used in this study: PCECV manufactured by Chiron Behring GmbH & Co. (Marburg, Germany), lot number 195011, with an antigen content of 9.16 IU per 1.0-ml ampoule; and PVRV manufactured by Aventis Pasteur (Lyon, France), lot number M0435, with an antigen content of 11.6 IU per 0.5-ml ampoule. In Thailand, a potency of at least 0.7 IU per 0.1 ml is required by the Ministry of Health for doses of rabies vaccine. Human rabies immunoglobulin (HRIG) was produced by Aventis Behring (Marburg, Germany) and administered at 20 IU per kg of body weight.

### Patient population

Two hundred and eleven patients from the Siriraj Hospital in Bangkok and the Bamrasnaradura Hospital in Nonthaburi, Thailand, participated in the study. All patients had WHO category II or III rabies exposures (*1*). Patients were included in the study if they had had contact with a known or suspected rabid animal less than 72 hours previously, except in the case of a bite to the face, hand, neck or fingers. In these cases, patients were included if they had presented for treatment within 24 hours of exposure.

Excluded from the study were patients with a history of rabies immunization or acute infectious disease; patients receiving immunoglobulins (other than HRIG), chloroquine or other antimalarial treatment; patients receiving specific anti-inflammatory drugs; and patients with an immunodeficiency or autoimmune disease. In all, 125 of the patients were treated with HRIG after admission to the hospitals, but these were randomly assigned to the three different study groups. Informed consent was obtained from all subjects prior to participation in the study which was approved by the Ethics Committee of the Faculty of Medicine, Mahidol University, Siriraj Hospital and by the Thai Ministry of Public Health.

### Postexposure treatment regimen

Prior to enrolment in the study, all patients were seen by physicians in the emergency rooms of the two hospitals. In each case, the physician made the decision to administer rabies postexposure treatment. Some of the patients were also treated with HRIG. If these patients were subsequently enrolled in the study they were randomly assigned to the three different study groups described below. On the day of enrolment into the study, a medical history was recorded for each patient that included the following: age, weight, height, sex, ethnic group and concomitant illnesses and/or treatment. The circumstances of the exposure, the site and type of the inflicted wound, the surgical procedures used (if applicable), the species and current status of the animal involved, and the laboratory results of rabies testing, if conducted, were also recorded.

Patients were randomly separated into three vaccination groups on a 1:1:0.625 Group 1/ Group 2/Group 3 basis. Prior to vaccination each patient was given a brief physical examination that included recording the oral body temperature, blood pressure, pulse rate and presence of concominant diseases. Group 1 received two 0.1-ml injections of PCECV intradermally on days 0, 3 and 7 and one 0.1-ml intradermal injection on days 30 and 90 following enrolment into the study. Group 2 was treated similarly, except that PVRV was used instead of PCECV. Group 3 was vaccinated intramuscularly with one 1.0 ml dose of PCECV on days 0, 3, 7, 14, 30 and 90 according to the Essen vaccination regimen. Injections were administered in the upper deltoid muscle or in the upper thigh. Blood samples were taken from each patient on days 0, 7, 14, 30 and 90, and the serum was assayed for the presence of rabies virus neutralizing antibody. Descriptions of wound healing were also recorded on days 3, 7, 14, 30, 40, 90 and 100. Wounds that did not heal properly were recorded as adverse events.

### Determination of rabies virus neutralizing antibody levels

Rabies virus neutralizing antibody (VNA) levels were measured by the rapid fluorescent focus inhibition test as described previously (*7*). The US standard rabies immunoglobulin (lot R-3) was titrated as a standard reference each time serum samples were tested. Identification of patient groups was withheld to conduct the assays blind. All serum samples were tested at Kansas State University. Rabies VNA titres were expressed as Geometric Mean Titres (GMTs) with range and were reported in IU/ml.

### Statistical analysis

This study was designed as a multicentre, controlled, stratified (by centre) investigation in which patients were randomized into three parallel vaccination groups (described above). The objective was to demonstrate that 0.1 ml intradermal injections of PCECV elicit rabies VNA levels on day 14 greater than or equal to 50% of the titre levels produced by 0.1-ml intradermal injections of PVRV (i.e. a non-inferiority hypothesis). After log-transformation of

the titre values, the hypothesis was tested by means of a one-sided *t*-test with a significance level of 2.5%. The lower one-sided 97.5% confidence intervals were calculated for the ratios of GMTs for Group 1/Group 3 and Group 2/Group 3. As required for non-inferiority hypotheses, the primary analysis was confined to the per-protocol population (*8*). Fifty-six of the 211 patients were excluded from the per-protocol population for one or more of the following reasons:

- the patient showed a pre-vaccination antibody concentration above the detection limit (27 patients);
- the vaccinations were not performed according to protocol (17 patients);
- the antibody determination on day 14 was not carried out, or was performed outside of the acceptable time window (11 patients);
- the patient had been treated with immunoglobulins, excluding HRIG (20 patients).

For the sake of calculation, antibody levels below the detection limit (< 0.05 IU/ml) were assigned a value of 0.025 IU/ml. An analysis of covariance was conducted to quantify the effect of potential prognostic factors, such as the vaccination group, the study centre, the sex, age (class) (less than 30 or above 30 years of age) of the patient, and whether the patient had had additional HRIG treatment.

# Results

## Patient population and demographics

All patients enrolled in the study presented for postexposure rabies treatment at either the Siriraj Hospital, Bangkok, Thailand (121 patients) or the Bamrasnaradura Hospital, Nonthaburi, Thailand (90 patients) between January and September 1997. The demographics of the patients are listed in Table 1. One hundred and eighteen patients had received wounds of WHO category III, 93 patients of WHO category II, and none of category I.

Concomitant diseases were reported in one patient from Group 1, four patients from Group 2 and four patients from Group 3. Concomitant diseases included acne, ulcer of the lower limbs, eczema, hyperlipidaemia, right-heel pain, hypertension and pyrexia. Medications administered to patients during the study included: tetanus toxoid, tetanus antiserum or tetanus immunoglobulin, antibiotics, analgesics and anti-acne preparations. Due to randomization these medications were distributed equally between the three vaccination groups.

## Exposures and wound treatment

As recommended by public health officials in Thailand, the patient's wounds were usually cleaned and washed at home, prior to arriving at the hospitals. More than 80% of all wounds had been inflicted by dogs, but other animals causing wounds included cats, rats, monkeys or squirrels. The presence of rabies virus was confirmed in only one dog that caused three exposures. The low rate of confirmed rabid animals was due to the recently changed public health recommendation to get postexposure vaccination as soon as possible. Previously, the animal had to be brought to the hospital for proof of rabies exposure.

More than 70% of the wounds occurred in the lower extremities. However, 12% of patients were bitten on the face, head, neck or fingers; these patients received treatment within 24 hours. Sixty-eight per cent of patients had incurred bleeding wounds at various body sites and surgical treatment was required for 13 patients. One of these patients required their wounds to be sutured. Of the 211 patients, HRIG (20 IU/kg of body weight) was infiltrated in and around the site of the wounds of 125 patients. The mean time intervals between exposure and vaccination were as follows: Group 1, 15.7 h (range 1–72 h); Group 2, 15.2 h (range 1–64 h); and Group 3, 16.9 h (range 1–64 h).

Table 1. **Patient population demographics**

| Group | Number of patients | Male/ female ratio | Mean age (years)[a] | Mean body mass index[a] (kg/m$^2$) |
|---|---|---|---|---|
| 1[b] | 79 | 29:50 | 25 (2–73) | 20.3 (12.8–28.6) |
| 2[c] | 75 | 21:54 | 28 (4–78) | 21.5 (8.9–31.8) |
| 3[d] | 57 | 28:29 | 33 (5–66) | 21.9 (13.3–33.3) |

[a] Values in parentheses are the range.

[b] Patients received 2 intradermal doses of 0.1 ml PCECV on days 0, 3 and 7; and 1 dose on days 30 and 90.

[c] Patients received 2 intradermal doses of 0.1 ml PVRV on days 0, 3 and 7; and 1 dose on days 30 and 90.

[d] Patients received 1 intramuscular dose of 1.0 ml PCECV on days 0, 3, 7, 14, 30 and 90.

## Determination of rabies VNA levels

The per-protocol population was defined with respect to the rabies VNA level determined on day 14 and comprised 155 patients. All patients who received the vaccines intradermally had rabies VNA levels of at least 0.5 IU/ml by day 14. On day 14 the GMT was 28.5 IU/ml and 28.9 IU/ml for Group 1 and Group 2, respectively. As the GMT ratio for the two groups was 0.99 (lower one-sided 97.5% confidence interval = 0.61) the two regimens could be considered equivalent ($P < 0.01$). The GMTs of the intradermal groups also did not differ significantly on days 7, 30, and 90.

On day 14, the GMT of patients that received the intramuscular vaccine (Group 3, 12.3 IU/ml) was lower than the GMTs of the intradermal Groups 2 and 3. On days 30 and 90, however, the GMT of Group 3 patients were higher than the GMTs of patients in the intradermal vaccination groups (Groups 1, 2; Table 2, Fig. 1). Two patients who received intramuscular PCECV injections had titres below 0.5 IU/ml on day 14. Both had received HRIG on the initial day of postexposure treatment. One of the patients was a late responder with a high titre of

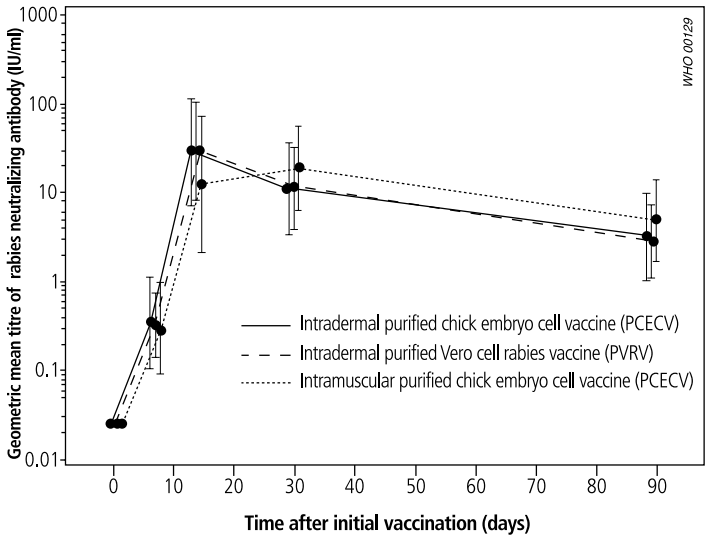
Table 2. **Rabies virus neutralization antibody titres for the per-protocol population**

| Day | No. of patients/GMT | Intradermal PCECV | Intradermal PVRV | Intramuscular PCECV |
|---|---|---|---|---|
| 7 | *n*[a] | 58 | 59 | 37 |
| | GMT (IU/ml)[b] | 0.34 (0.05–19.1) | 0.32 (0.1–2.2) | 0.29 (<0.05–19.1) |
| 14 | *n* | 59 | 59 | 37 |
| | GMT (IU/ml) | 28.5 (1.1–1318.0) | 28.9 (1.6–350.0) | 12.3 (0.4–301.0) |
| 30 | *n* | 55 | 57 | 36 |
| | GMT (IU/ml) | 10.9 (1.5–171.0) | 10.9 (0.6–157.0) | 18.5 (0.5–217.0) |
| 90 | *n* | 53 | 58 | 36 |
| | GMT (IU/ml) | 3.0 (0.4–59.1) | 2.7 (0.5–47.0) | 4.7 (0.5–60.9) |

[a] *n* = the number of patients per protocol.

[b] GMT = geometric mean titre of rabies virus neutralizing antibodies. Values in parentheses are the range.

Fig. 1. **Concentration of rabies neutralizing antibody (per protocol population)**




11.3 IU/ml on day 30. The other patient developed a titre of 0.5 IU/ml by day 30, but this remained at 0.5 IU/ml even on day 90.

In the analysis of covariance which was conducted on the per-protocol population, vaccination group, medical centre, sex, age (class) and use of HRIG were included as main factors. As the WHO exposure category and HRIG administration were highly dependent, only the latter factor was included in the model. A noticeable effect of medical centre, sex and HRIG administration was found with regard to the day 14 antibody level. Patients treated at the Bamrasnaradura Hospital had 2.2-fold higher rabies VNA levels than patients treated at the Siriraj Hospital. We also found that female patients tended to have 55% of the rabies VNA levels observed in male patients; and patients receiving HRIG also showed lower (54%) rabies VNA levels than patients who did not receive HRIG. In a supportive analysis we also evaluated all vaccinated patients who had a day 14 antibody determination ($n = 203$) and reached a similar result as for the per-protocol population. The ratio of rabies VNA levels for Group 1 and Group 2 was 0.99, and the lower one-sided 97.5% confidence interval was 0.64.

### Adverse reactions

Adverse reactions were reported more frequently in patients who received intradermal injections of PCECV (48%) or PVRV (51%) compared to patients who received intramuscular injections of PCECV (33%). Reported adverse reactions in decreasing order of frequency of occurrence included: erythema, pain and/or swelling at the site of injection, and fever.

## Discussion

All of the patients enrolled in this study had been bitten by potentially rabid animals in Thailand and were at risk of contracting and dying of rabies. Eighty percent of the wounds were inflicted by dogs, the main reservoir for rabies in Thailand. It has been reported previously that 9–18% of those exposed to rabid animals will die without postexposure treatment (*9*). In Thailand, the incubation period for developing clinical rabies in an untreated infected person is short, with a mortality rate of approximately 71% within one month of exposure and 87% within three months (*10*).

In our study no deaths occurred in any group, indicating that intradermal injections of 0.1 ml PCECV provided the same protection rate as intradermal injections with 0.1 ml PVRV or with intramuscular injections of PCECV. The titres in patients who received intradermal injections of PCECV and PVRV were virtually indistinguishable, indicating that there was equality in the immune response to either vaccine in patients presenting with WHO category II and III exposures. Compared with earlier studies the antigenic contents of the vaccines was higher than the minimum WHO requirement of 2.5 IU per dose, as measured by the NIH test (*1*). Nevertheless, we used typical commercial vaccine lots and the rabies VNA response is certainly high for all three vaccination groups. Although this result cannot be generalized to a lower potency vaccine, lower potency vaccines were used in earlier studies and elicited a satisfactory rabies VNA response (*2*, *4–6*).

After exposure to a potentially rabid animal, it is desirable to elicit an immune response as quickly as possible to give the patient the best opportunity for survival. The highest antibody titres in the early phase were produced in patients who received 0.1 ml intradermal injections of PCECV or PVRV by the 2-site regimen recommended by the WHO for postexposure treatment (*3*). By day 14 the GMTs in patients who had received the intradermal PCECV and PVRV injections were higher than those produced by the Essen regimen using intramuscular injections of PCECV. After day 14, however, the rabies VNA levels of patients who received intramuscular injections of PCECV were higher than

those in patients who received PCECV or PVRV intradermally.

There were more adverse reactions reported by patients receiving intradermal injections of PCECV and PVRV than reported by patients who received PCECV intramuscularly. However, there was no significant difference between the number of adverse reactions reported by patients who received PCECV and PVRV intradermally. All of the adverse reactions occurred at the site of injection, were mild and typical of those reported by other intradermal vaccine studies (*4–6*), and were resolved without treatment. Intradermal vaccination with PCECV was therefore safe and well tolerated.

In conclusion we have demonstrated that PCECV is a highly immunogenic vaccine when administered in 0.1-ml intradermal doses according to the WHO recommendations for postexposure treatment of patients with WHO category II and III rabies exposures. The WHO intradermal regimen for postexposure treatment with PCECV requires only 15% of the amount of vaccine needed to treat a patient by the Essen intramuscular regimen. Clearly this makes the intradermal regimen an attractive option for physicians in developing countries with limited resources. By significantly reducing the cost of postexposure treatment in developing countries, more patients will be able to afford purified tissue culture vaccine, and will not have to suffer the vaccination reactions and failures associated with the older but less expensive nerve cell vaccines.

If intradermal treatment is used, it is of paramount importance that the medical staff be proficient in the administration of intradermal vaccines. Using aseptic techniques, a 0.1 ml dose of vaccine may be withdrawn from a vial and the remainder used for another patient, provided that the vial is stored in a refrigerator at 2–8 °C (temperature range recommended by manufacturer) and that a sterile needle and syringe is used to draw vaccine for each patient. Reconstituted vaccines should be used as soon as possible and those without preservative, such as PCECV and PVRV, must be used within 6–8 h if kept at 2–8 °C. The intradermal method is particularly appropriate where vaccine or money are in short supply, and in centres dealing with large numbers of bitten patients daily, where there is an established cold chain and well-trained staff. ■


## Résumé

### Réponse en anticorps après vaccination antirabique de post-exposition par de petites doses intradermiques de vaccin purifié préparé sur cellules d'embryon de poulet ou sur cellules Vero

L'introduction de vaccins préparés sur cultures tissulaires a permis d'améliorer considérablement l'immunogénicité et l'innocuité de la vaccination antirabique, mais ces vaccins sont souvent d'un coût prohibitif pour les pays en développement. Afin d'examiner la possibilité de réduire le coût de la vaccination antirabique de post-exposition en utilisant de plus petites doses de vaccin, nous avons étudié l'innocuité et l'immunogénicité de doses de 0,1 ml de vaccin purifié préparé sur cellules d 'embryon de poulet (PCECV), administrées par voie intradermique à des patients potentiellement exposés au virus rabique. L'étude portait sur 211 patients admis dans deux hôpitaux de Thaïlande pour une exposition à la rage de catégorie II et III selon la classification de l'OMS. Des immunoglobulines antirabiques humaines ont été administrées à 125 d'entre eux, puis les 211 patients ont été répartis par tirage au sort dans trois groupes de traitement. Le groupe 1 était vacciné par voie intradermique avec 0,1 ml de PCECV en deux sites les jours 0, 3 et 7 et en un site les jours 30 et 90. Le même schéma de vaccination par voie intradermique a été appliqué au groupe 2, mais avec le vaccin antirabique purifié préparé sur cellules Vero (PVRV). Le groupe 3 était vacciné par voie intramusculaire en un site avec 0,1 ml de PCECV les jours 0, 3, 7, 14, 30 et 90. Les injections étaient pratiquées soit dans le deltoïde soit dans la partie antérolatérale de la cuisse. Des échantillons de sang ont été prélevés les jours 0, 3, 7, 14, 30 et 90 et on a recherché dans le sérum la présence d'anticorps neutralisants dirigés contre le virus rabique. Le jour 14, les patients vaccinés par voie intradermique avec le PCECV et le PVRV présentaient les mêmes titres d'anticorps neutralisants. Bien que les réactions indésirables aient été plus fréquemment rapportées chez les patients vaccinés par voie intradermique, elles étaient associées à la voie d'administration et il n'y avait pas de différence significative du nombre de réactions indésirables rapportées chez les patients ayant reçu le vaccin PCECV et chez ceux ayant reçu le vaccin PVRV par cette même voie. Nous concluons que le PCECV est un vaccin sans danger et hautement immunogène pour la vaccination de post-exposition lorsqu'il est administré en doses de 0,1 ml selon la méthode d'injection intradermique en deux sites (« 2,2,2,0,1,1 ») recommandée par l'Organisation mondiale de la Santé.

## Resumen

### Respuesta de producción de anticuerpos tras la vacunación antirrábica postexposición con pequeñas dosis intracutáneas de vacuna antirrábica purificada obtenida a partir de células embrionarias de pollo o de células Vero

Las vacunas basadas en cultivos tisulares han mejorado espectacularmente la inmunogenicidad e inocuidad de la vacunación antirrábica, pero son a menudo prohibitivamente caras en los países en desarrollo. A fin de

determinar si se podía reducir el costo de la vacunación antirrábica postexposición usando dosis más pequeñas de vacuna, analizamos la inocuidad y la inmunogenicidad de una alícuota de 0,1 ml de vacuna purificada obtenida mediante células embrionarias de pollo (VPCEP) administrada intracutáneamente a pacientes que podían haber estado expuestos al virus de la rabia. El estudio abarcó a 211 pacientes que acudieron a dos hospitales de Tailandia con exposiciones a la rabia clasificables en las categorías II y III de la OMS. Se administró inmunoglobulina humana contra la rabia a 125 de los pacientes, y a continuación se asignó aleatoriamente a todos ellos a alguno de los tres grupos establecidos. A los pacientes del grupo 1 se les vacunó intracutáneamente con 0,1 ml de VPCEP en dos puntos del cuerpo los días 0, 3 y 7, y en un punto los días 30 y 90. El grupo 2 fue sometido a ese mismo régimen de vacunación intracutánea, pero en lugar de VPCEP recibió 0,1 ml de vacuna antirrábica purificada obtenida mediante células Vero (VPCV). El grupo 3 fue vacunado intramuscularmente en un punto con 1,0 ml de VPCEP los días 0, 3, 7, 14, 30 y 90. La inoculación se practicó en la parte superior del músculo deltoides o bien en la parte superior del muslo. Se obtuvieron muestras de sangre los días 0, 3, 7, 14, 30 y 90, analizándose el suero en busca de anticuerpos neutralizadores del virus de la rabia. El día 14, los pacientes vacunados intracutáneamnete ya fuera con VPCEP o con VPCV presentaban los mismos títulos de anticuerpos neutralizadores del virus de la rabia. Aunque las reacciones adversas fueron más frecuentes en los pacientes sometidos a inoculación intracutánea, dichas reacciones estaban asociadas a la vía de inyección; no se observó una diferencia importante en el número de reacciones adversas entre los pacientes que habían recibido VPCEP por vía intracutánea y los que habían recibido VPCV por esa misma vía. Nuestra conclusión es que la VPCEP es una vacuna inocua y altamente inmunogénica para la vacunación antirrábica postexposición cuando se administra en dosis de 0,1 ml empleando el método de inyección intracutánea en dos puntos («2,2,2,0,1,1») recomendado por la Organización Mundial de la Salud.

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