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Original Article

Rabies post-exposure prophylactic vaccination for returning travelers to Japan☆

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ABSTRACT

Background: Rabies post-exposure prophylaxis (PEP) in Japan is administered using 6 subcutaneous doses (on days 0, 3, 7, 14, 30, and 90), which is not in line with international recommendations of 4 or 5 intramuscular doses. For reducing dose frequency, we evaluate the immunogenicity of PEP with a regimen of 6 subcutaneous doses.
Method: This prospective single-center cross-sectional study was performed between September 2013 and December 2014. We included patients underwent rabies PEP by purified chick embryo-cultured rabies vaccine Kaketsuken (PCEC-K) at our clinic, and excluded patients with a history of pre-exposure prophylaxis or PEP using rabies immunoglobulin. The rabies virus-neutralizing antibody tests were performed at the first visit to our office (doses 1–4) and at the fifth and sixth doses.
Results: Data were available for 43 of 59 enrolled patients. Thirty-two patients did not start PEP within 48 h after exposure to animals. The seroprotection rates (≥0.5 IU/mL) were 90.7% and 75.7%, at days 30 and 90, respectively. Despite receiving a fifth dose, 85.3% of the patients exhibited decreasing antibody titers during days 30–90 ($p < 0.001$).
Conclusions: The seroprotection rates of PCEC-K induced subcutaneously were insufficient to prevent rabies at day 30 and 90.
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1. Introduction

A World Health Organization (WHO) position paper described methods for reducing the use of rabies post-exposure prophylaxis (PEP) in resource-limited countries [1]. On this paper, 4 intramuscular doses or 3 intradermal doses are recommended for rabies post-exposure prophylaxis (PEP) [1]. Although there are no formal immunological correlates of protection, the WHO criterion for adequate immunogenicity is a titer of at least 0.5 IU/mL on day 14 of the PEP. In contrast, the purified chick embryo-cultured rabies vaccine from Kaketsuken (PCEC-K) developed in Japan is approved for PEP using 6 subcutaneous doses (on days 0, 3, 7, 14, 30, and 90), which is different from the global standard protocol recommended by the WHO [1]. Although it was not well known that a 6th dose was needed for PEP by PCEC-K, Takayama et al. reported that 72 patients had antibody titers of >1.0 equivalent unit/mL at 2–4 weeks after the 5th dose of PEP by PCEC-K [2], and this result indicated that the doses of PEP by PCEC-K may be reduced to 5 doses. However, these results were not the primary outcome of that

Abbreviations: WHO, World Health Organization; PEP, rabies post-exposure prophylaxis; PCEC-K, purified chick embryo-cultured rabies vaccine from Kaketsuken; RIG, rabies immunoglobulin; GMT, geometric mean titers.

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study, and another study reported that 10% of 30 patients had antibody titers of <0.5 IU/mL at 2–8 weeks after the 5th dose of PEP with PCEC-K [3]. Therefore, this study aimed to better understand the adequacy of the current administrative schedule approved for PEP in Japan, specifically to evaluate whether the 5th or 6th dose of PEP with PCEC-K can be omitted.

2. Patients and methods

This prospective single-center cross-sectional study was performed at the travel clinic of the National Center for Global Health and Medicine, which is visited by over 700 patients for post-travel consultation annually. Between September 1, 2013 and December 31, 2014, we enrolled patients older than 16 years old, who had been exposed to animals in foreign countries, and who had undergone rabies PEP at our travel clinic. We excluded patients who had any previous rabies vaccination, or had received PEP via intradermal administration, via intramuscular administration on an abbreviated multisite schedule (2-1-1), using rabies immunoglobulin (RIG), or not following regular schedules. We administered rabies PEP subcutaneously with PCEC-K (Kaketsuken, 1.0 mL, lot numbers RB18–RB20) with the approved schedule for the vaccine (on days 0, 3, 7, 14, 30, and 90). The potency of these vaccines satisfied the international level of standard rabies vaccine (over 2.5 IU/vial). If the patient had started PEP before returning to Japan, we continued the remaining doses of PEP using PCEC-K.

We recorded the patients' clinical information, which included age, sex, underlying disease(s), animals involved, WHO exposure category, country of exposure, date of exposure, days of first hospital visit after exposure, and brand name of the rabies vaccine for previous PEP. “Appropriate timing” for PEP was defined as starting PEP within 2 days after exposure. Blood tests were performed at the first visit to our office (doses 1–4) and at the fifth and sixth doses. Rabies virus-neutralizing antibody responses were measured using rapid fluorescent focus inhibition with some modification [4–6]. As the quantitation limit for this test is 0.1 IU/mL, results of less than 0.1 IU/mL were defined as negative. Seroprotective antibody titers were defined as $\geq$ 0.5 IU/mL [1]. If a patient had low antibody titers (<0.5 IU/mL) at the sixth dose, we performed an additional blood test for antibodies to the rabies virus at 4–8 weeks after the sixth dose.

This study was approved by the Research Ethics Committee of the National Center for Global Health and Medicine (NCGM-G-001475-01). All patients provided informed consent prior to the data collection and analysis.

2.1. Statistical analysis

The patients' data were analyzed using SPSS software (version 24.0; IBM Corp., Armonk, NY, USA). Patients were divided into 2 groups based on their receiving PEP using only PCEC-K or other rabies vaccines and PCEC-K. Continuous variables (e.g., age and antibody titers) were compared using the Mann-Whitney *U* test, and Fisher's exact test was used to compare categorical variables (e.g., sex, animal involved, adequate timing of PEP, place of exposure, and WHO category of exposure) with an α level of 0.05. The difference in the antibody titers at the fifth and sixth doses was evaluated using the Wilcoxon signed-rank test ($\alpha = 0.05$). GraphPad Prism (version 6.05; GraphPad Software, Inc., San Diego, CA, USA) was used to plot antibody titer values.

3. Results

Among the 59 patients who were enrolled, 43 patients (23 men, median age: 32 years) had available data (Table 1). Sixteen patients were excluded due to loss to follow-up (8 patients), previous rabies immunization (4 patients), intradermal administration (1 patient), an abbreviated multisite schedule (1 patient), using RIG (1 patient), and an irregular vaccination schedule (1 patient). Only 2 patients had a history of malignant disease (1 malignant lymphoma and 1 cervical cancer), which had been successfully treated; none of the patients received immunosuppressants. Thirty-three patients (76.7%) were exposed to animals in Asia, including 7 patients in Thailand, followed by 6 patients in India. The median time to administration after exposure was 4 days (range: 0–144 days; interquartile range [IQR]: 1–7 days). Among the patients who did not undergo PEP within 2 days after exposure, 14 patients (58.3%) had WHO category 3 exposure to animals. The 11 patients who started PEP abroad took a median 1 dose (IQR: 1.0–2.8) of non-PCEC-K vaccine. Among the participants, 5 patients received WHO prequalified vaccines (Verorab™ in 2 patients and Rabipur™ in 3 patients), 5 patients received WHO's non-prequalified vaccines, and 1 patient did not have information to verify the brand received.

The geometric mean titers (GMT) for antibodies to the rabies virus were 1.90 IU/mL and 1.09 IU/mL at the fifth and sixth doses, respectively (Table 2). Compared to 11 patients who received both PCEC-K and non-PCEC-K rabies vaccines, 32 patients who completed PEP with only PCEC-K exhibited significantly lower titers at the fifth and sixth doses ($p = 0.001$ and $p = 0.013$, respectively). Despite receiving 5 doses, 85.3% of the patients exhibited a significant decrease in their antibody titers between the fifth and sixth doses ($p < 0.001$, Fig. 1). Ten patients did not exhibit seroprotective titers ($\geq$0.5 IU/mL), even 2 months after receiving 5 doses of rabies vaccine. Although we could measure the antibody titers in 3 of these 10 patients after the sixth dose, only 1 patient exhibited seroprotective titers (0.62 IU/mL). After receiving PCEC-K, 4 patients experienced mild local reactions (e.g., swelling and redness at the injection site), and 1 patient experienced mild urticaria that resolved after short-term anti-histamine treatment. There was no report that the participants of this study had developed rabies up to April 30, 2016.

4. Discussion

In this study, the evidence for decreasing 6 doses to 4 or 5 doses of PEP by PCEC-K might not be supported because of the low seropositivity rate of PEP by PCEC-K with rapidly waning immunity. Preferred PEP regimens have been previously assessed for clinical outcome, feasibility, cost-effectiveness and immunogenicity. Of these, the immunogenicity is an important indicator for adjusting the dose of PEP [7]. In our study, 10% of the patients who received the PCEC-K vaccine did not achieve seroprotective titers, and the GMTs for PEP using only PCEC-K were significantly lower than the GMTs for PEP using PCEC-K after receiving other rabies vaccines. The GMTs after PCEC-K vaccination were relatively low in the present study, compared to the previous reports of PEP immunogenicity after the intramuscular administration of other purified chick embryo cell-cultured rabies vaccine [8] or a purified Vero cell-cultured rabies vaccine [9] without RIG. In those studies, the reported GMTs were 10.3 IU/mL and 14.9 IU/mL at day 28, and 4.9 IU/mL and 3.4 IU/mL at day 90, respectively. There are few reports regarding subcutaneous immunization using PCEC-K, although only 3 of 30 Japanese patients in one study exhibited low titers (<0.5 IU/mL) at 2–8 weeks (day 44–86) after their fifth dose of PCEC-K [3]. In another report, no patients exhibited low titers (<1.0 equivalent units/mL) at 2 weeks after their fifth dose (day 44) [2]. However, the timing of the serum sampling in those two studies was different from our study, which followed the WHO's recommended schedule (antibody testing at days 0, 14, 28/30, 90, 180, and 360) [10]. In these previous studies, assessment of the

Table 1
Characteristics of patients who received rabies post-exposure prophylaxis.

	All	PCEC-Konly	Subsequent administration of PCEC-K after other vaccines
n	43	32	11
Median age, years (range) [IQR]	32 (18–75) [25–40]	32 (20–75) [27–40]	29 (18–48) [22–40]
Sex, male	23	17	6
Animals involved			
Dogs	20	12	8
Cats	9	8	1
Monkeys	8	7	1
Others	5	5	0
Place of exposure			
Asia	23	13	10
Africa	2	2	0
Other	8	7	1
WHO exposure category			
1	2	1	1
2	17	15	2
3	24	16	8
Starting PEP within 2 days after exposure	19	[a]10 (23.3%)	[a]9 (81.8%)
Doses of vaccine except for PCEC-K	-	–	1 dose: 6 2 doses: 2 3 doses: 3

PCEC-K, purified chick embryo-cultured rabies vaccine, Kaketsuken; IQR, interquartile range; WHO, World Health Organization; PEP, post-exposure prophylaxis.
[a] Significant difference between 2 groups ($p < 0.001$, Fisher's exact test).

Table 2
Neutralizing antibody titers in patients.

	Day 0	Day 3	Day 7	Day 14	Day 30	Day 90
All, n	20	17	2	4	43	43
GMT, IU/mL	0.00	0.00	0.59	2.58	1.90	1.09
[a]Protection rate, %	0	0	50	75	90.7	76.7
PCEC-K only, n	20	11	0	1	32	32
GMT, IU/mL	0.00	0.00	–	0.48	1.45	0.93
Protection rate, %	0	0	–	0	87.5	68.7
Subsequent administration of PCEC-K after other vaccines, n	0	6	2	3	11	11
GMT, IU/mL	–	0.00	0.59	4.53	4.10	1.72
Protection rate, %	–	0	50	100	100	100

[a] Protection rate was defined as the proportion of patients whose antibody titers were >0.5 IU/mL. GMT, geometric mean titer; PCEC-K, purified chick embryo-cultured rabies vaccine, Kaketsukenx

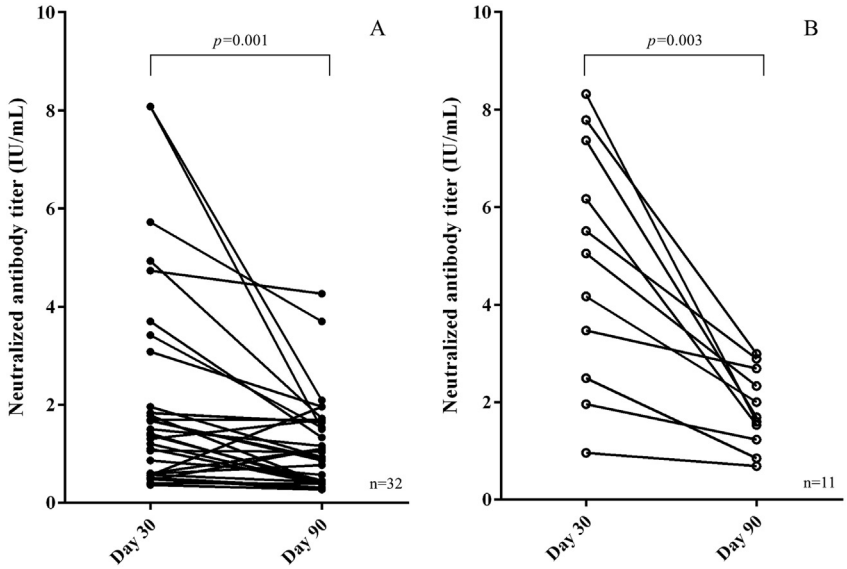

Fig. 1. Changes in rabies virus-neutralizing antibody titers from day 30 to day 90. The rabies virus-neutralizing antibody response was measured using rapid fluorescent focus inhibition, separate administration of PCEC-K alone as A (n = 32), or subsequent administration of PCEC-K after other vaccines as B (n = 11). The difference in the antibody titers between the fifth and sixth doses was evaluated using the Wilcoxon signed-rank test ($\alpha = 0.05$).

immunogenicity of PCEC-K, ELISA kit (DIAGNOSTICS, Pasteur, France) was substituted for rapid fluorescent focus inhibition [2,3]. It was reported that there was a correlation between neutralization and ELISA antibody titers measured by the same ELISA kit ($r = 0.697$) [11]. Additionally, because the neutralizing antibody titers were higher than ELISA antibody titers for most of the serum samples in the same report, the difference in the method used to measure antibody titer may not account for the low immunogenicity in our study.

The immune response to vaccination is generally influenced by many factors, which include the presence of maternal antibodies, the quantity of the antigen in a dose, the route of administration, the presence of an adjuvant, and host factors (e.g., age, nutritional factors, genetic factors, and coexisting disease) [12]. In the previous study of pre-exposure rabies immunization by human diploid cell vaccine or the two kinds of purified chick embryo cell vaccine, immunogenicity of rabies vaccine was affected by gender, body mass index, interval between the first and third doses of vaccine, and vaccine manufacturer [13]; however, these factors were not associated with low immunogenicity [14,15]. Generally, the only clinical situation where inadequate titers may be seen is when subjects are immunocompromised due to a medical condition or the use of immunosuppressive agents [16]. In our study, the appropriate cold chain was maintained, the vaccine was properly provided, and only 2 participants had underlying disease. In a previous study using PCEC-K in Thailand, PCEC-K without RIG provided higher GMT (5.56 IU/mL and 5.12 IU/mL at days 30 and 90, respectively) when administered intramuscularly, not subcutaneously [15]. According to this result, the low immunogenicity may be related to the administration route. Similarly, subcutaneous immunization provided a lower response to the hepatitis B vaccine, compared to intramuscular administration [18,19]. However, it was mentioned that inadvertent subcutaneous administration did not reduce immunogenicity by using purified Vero cell-cultured rabies vaccine [20,21]. Therefore we cannot conclude that the administration route causes the low immunogenicity.

In the present study, a decrease of approximately 40% in the GMTs was observed between days 30 and 90, despite administering a fifth dose of the rabies vaccine. However, it is unknown whether waning anti-rabies antibody titers decrease the effectiveness of rabies prevention, and decreases of 8–77% between day 30 and day 90 have been reported in previous studies [8,9,17]. Given the low seropositivity rate of PEP by PCEC-K with rapidly waning immunity, decreasing 6 doses to 5 doses of PEP might not be worth the risk of contracting rabies.

The present study revealed that approximately 60% of the patients with animal exposure did not receive PEP within the appropriate period. Only 31.9% of the patients with animal exposure had received in-hospital PEP in the country of their exposure. Even among 27 patients with WHO category 3 exposure, only 59.2% of the patients had started PEP while abroad. In other countries including New Zealand, which is a rabies-free country similar to Japan [22–25], 52.2–78.5% of exposed patients received their first vaccine injection in the country of their exposure. The median time from exposure to the first PEP dose was 1 day (IQR: 0–7 days) in the UK [22], and the average time was 1.8 days in the Republic of Korea [23]. The reason that many Japanese patients delayed starting PEP may be associated with lack of knowledge regarding rabies, as several reports showed that most Japanese travelers do not attend pre-travel consultations and are indifferent regarding travel health. For example, only 5% of Japanese travelers who visited a hospital in Nepal had been vaccinated against hepatitis A or typhoid [26], and another study found that only 2% of Japanese travelers sought advice from a travel clinic [27]. In Japan, it is important to educate travelers going to rabies-endemic countries regarding the appropriate timing of PEP. Moreover, the fact that RIG is not available in Japan should be emphasized for Japanese travelers, so that if necessary they do not miss receiving appropriate PEP in a country where RIG is available, before returning Japan.

4.1. Limitations

Some limitations exist in this study. First, the sample size is too small. We were not able to perform parametric tests which has more power than non-parametric tests, and not to assess the factor of low immunogenicity. However, it is enough to show the immunogenicity of PEP by PCEC-K in this study. Secondly, there was no comparison group of travelers who had received the WHO prequalified vaccine according to the preferred regimen. Analyzing the reasons underlying the low immunogenicity showed by PCEC-K in this study will be an important future research aim. Finally, we were able to perform the additional antibody titer test after the 6th dose for only 3 of patients who did not exhibit seroprotective titers at day 90 (30%). Of these, 2 patients did not exhibit seroprotective titer despite 6th dose. Therefore, it was unclear whether 6th immunization by PCEC-K was effective to get seroprotective titer for the other 7 patients.

In conclusion, because PCEC-K provided low levels of immunogenicity, the sixth dose of PEP by PCEC-K should be continued. Although the reason for low immunogenicity of PEP is not well known, it may be related to the subcutaneous administration route. Further studies are needed to evaluate the immunogenicity of PEP by PCEC-K via both intramuscular and subcutaneous administration by comparison with a control group.

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Authorship statement

All authors meet the ICMJE authorship criteria as below.

(1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data: Kei Yamamoto, Yasuyuki Kato, Mugen Ujiie
(2) drafting the article or revising it critically for important intellectual content: Kei Yamamoto, Yasuyuki Kato, Mugen Ujiie, Akira Noguchi, Satoshi Inoue
(3) final approval of the version to be submitted: Kei Yamamoto, Mugen Ujiie, Akira Noguchi, Yasuyuki Kato, Yoshihiro Fujiya, Momoko Mawatari, Satoshi Kutsuna, Nozomi Takeshita, Kayoko Hayakawa, Shuzo Kanagawa, Satoshi Inoue, Shigeru Morikawa, Norio Ohmagari.

Conflict of interest/disclosure

The authors have declared no conflicts of interest.

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