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Serological Response of Pups to the Selected Canine Vaccines and Vaccination Schedules against Canine Parvovirus

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Abstract : This study was undertaken to provide the appropriate vaccination protocol of canine parvovirus (CPV) vaccine for the companion dogs in Korea. A total of 120 healthy pups (20 pups per group) at 6 weeks of age were randomly assigned to one of four commercially available vaccines [C, G, K, and V groups] and one of vaccination schedules [V2 and V4 groups]. The serological responses to the CPV component of the vaccines were determined by measuring HI titers. The maternal antibodies was declined to under the protective level at 6 weeks of age. Therefore, it was considered that vaccination of pups for CPV should be started at 6 weeks of age. And when the combination vaccine was used, the immunogenicity of V vaccine was superior to the other vaccines and optimum vaccination schedule was 3 times vaccination with 3 weeks-interval starting vaccination at 6 weeks of age. Although pups were vaccinated at 6 weeks of age, the geometric mean CDV titers of pups in all groups by 9 weeks of age were under the protective level. So, hygienic measures including avoiding to exposure to the high risk areas were needed to prevent CPV infection in this period.

Key words **:** canine parvovirus, vaccine, vaccination schedule, HI titer

Introduction

Canine parvovirus (CPV) infection in dogs has been associated with outbreaks of acute hemorrhagic enteritis characterized by bloody diarrhea, vomiting, depression, leukopenia, and dehydration[23]. The causative organism, CPV type 2 (CPV-2), was first identified in 1979[1]. Since then, two variants of the virus have been identified: CPV type 2a (CPV-2a) in 1980 and CPV type 2b (CPV-2b) in the mid 1980s[20]. Currently, more than 80% of all cases of CPV infection in the United states are a result of infection with CPV-2b[19].

At the present time, nearly all adult dogs are immune because of vaccination or natural exposure[16,28]. Although vaccination has reduced the number of clinical cases, parvoviral enteritis is still an important disease, especially in pups. The continuance of the disease might be the result of the mutation of the virus; but it is not likely, because vaccines made from CPV-2 produce an antibody response that protects dogs challenge with CPV-2a and CPV-2b8. And pups are at risk for infection because maternal antibodies interfere with response to vaccines but do not protect the pup from natural disease[11,21].

Even with adequate treatment, the motality for dogs with CPV infection is high[7,14]. For this reason, extensive efforts have been directed at preventing the disease through vaccination. The original vaccines incorporated feline panleukopenia virus or mink enteritis virus, and viruses that are antigenically similar to CPV-2 were of limited efficacy[22]. Killed virus and modified-live CPV vaccines were subsequently developed; however, efficacy varied widely[13,17]. In addition, it was found that maternally derived antibody titers that were too low to provide protection from naturally acquired infection were high enough to prevent immunization[18,21]. Thus, dogs were susceptible to infection for as long as 10 weeks, while passive (i.e., maternally derived) immunity waned and before active immunity could be induced[13].

In some instances, pups could not be actively immunized with conventional, commercial vaccines until at least 18 weeks of age. Thus, veterinarians recommend administration of multiple CPV vaccine doses. However, a pup would develop clinical CPV enteritis if exposure occurs during the window of susceptibility[3,24]. The window of susceptibility exists because modified live CPV is less immunogenic than naturally occuring strains[3]. This is a result of the viral attenuation process, which reduces CPV host infectivity[23]. The more passages CPV undergoes in tissue culture, the less infective it is *in vivo*. To more effectively overcome interfering levels of maternally derived antibodies, a new vaccine was developed containing a low-passage CPV strain with inherently greater host infectivity. To further enhance its immunogenicity, the low-passage CPV strain was produced in a high-titer dosage (i.e. with an increased amount of CPV)[6,17]. High-titer canine parvovirus vaccines are intended for use in the one segment of the canine population that continues to be vulnerable to clinical CPV enteritis - pups four to 18 weeks of age[10,23].

Despite high-titer vaccines were available, manufactures of these commercial vaccines recommended that pups be vaccinated until they are 16 weeks of age or older. However, recently after high-titer vaccines are available commonly, vaccination schedules have been changed so that most pups receive their last dose of CPV vaccine at 12 weeks of age[12,26].

Recently in Korea, CPV infection in the companion dogs has been controlled after use of high-titer CPV live vaccines.

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However, CPV infection is quite common in kennels and breeding farms. And difference in efficacy of vaccines is anticipated because of use of various vaccines and vaccination protocols. Thus, this study was undertaken to compare the efficacy of four commercially available combination vaccines and three different vaccination schedules in inducing an active immune response in pups against CPV.

Materials and Methods

Experimental animals

1) Efficacy of vaccines

To compare the efficacy of four commercially available combination vaccines and three vaccination schedules in inducing an active immune response in the companion dogs against CPV, a total of 120 healthy pups at 6 weeks of age were included in this study. These pups were presented for vaccination by owner at 9 local animal clinics between March, 2002 and October, 2002. After owner's were in compliance with participation in this study, pups at six weeks of age (20 pups per group) were randomly assigned to one of six groups shown in Table 1. Each pup was reared in owner's house and managed according to the ownership. The pups received preventive and therapeutic medical care as deemed necessary by the veterinarians at local clinics. This included anthelmintics and rabies vaccination. The eleven pups failed to complete the study and were excluded during the trial.

2) Change of maternal antibodies

Seven healthy mixed breed pups were used to observe the declining pattern of maternal antibodies. These pups were born from a bitch who was vaccinated 2 times with the commercial combination vaccine containing CPV at 6 month interval before pregnant, and were reared for 7 weeks with the dam. Pups were weaned at 7 weeks of age and managed in individual cage and provided with commercial dog food and fresh water ad libitum during the experimental period of 17 weeks of age. Blood were collected every week for entire period. In this study, antibody titers of 1:80 or greater using hemagglutination inhibition (HI) were considered to be protective.

Table 1. Numbers of pups, number of vaccinations, and interval of vaccination in each vaccine group

Groups		Number of pups	Number of vaccination	Interval of administration (Weeks)
Vaccine	C	20(18)*	3	3
	G	20(18)	3	3
	K	20(17)	3	3
	V (or V3)	20(20)	3	3
Interval	V 2	20(19)	5	2
	V 4	20(17)	3	4
Total	6 groups	120(109)		

*The number in parenthesis is number of pups which were provided all data and finally used for statistical analysis.

Vaccines

The two commercial combination vaccines (G and K) were manufactured in Korea and two vaccines (C and V) were imported from USA. Each vaccine was contained modified-live CPV, canine distemper virus, canine adenovirus type 2, and canine parainfluenza virus in a lyophilized form and *Leptospira canicola-icterohaemorrhagiae* bacterin in a liquid form that was used as the vaccine diluent. All vaccines were purchased by the investigators.

At six weeks of age, each pup in each group was vaccinated with one of the vaccines according to Table 1. Revaccination was administered at 8, 9, 10, 12, and 14 weeks of age according to Table 1. Vaccines were administered subcutaneously in the dorsal aspect of the neck or thorax. Postvaccinal adverse effects were not observed in all vaccine groups.

Hemagglutination inhibition (HI) test

The HI test was based on the method described by Carmichael *et al*[4]. Briefly, after heat inactivation at 56°C for 30 minutes, the sera were treated with pig erythrocytes to remove non-specific inhibitors of viral hemagglutination. Serial two-fold dilutions of the treated sera were prepared in U-bottomed microtiter plates and then an equal volume (50 μl) of virus suspension, containing 8 hemagglutination units of CPV, was added to each well. When the serum-virus mixtures had been incubated for 60 minutes at room temperature, 50 μl of 0.5 percent pig erythrocytes was added to each well and the plates were kept at 4°C for four hours.

The antibody titer was considered to be the reciprocal of the highest dilution that completely inhibited hemagglutination. In each test, known negative and positive sera with moderate and high titers were included. Results were only accepted when the titers of the standard sera fell within specific limits (a two-fold change for the positive sera). Seroconversion was considered to be a four-fold or greater change in titer or an increase from a negative value (<8) to a positive value (8 or more).

Statistical analysis

Prior to statistical analysis, all titers were converted to natural logarithms and geometric mean CPV HI titers were determined for each sample period. And the week that each pup seroconverted, the overall percentage of pups in each group that had seroconverted at each sample period, and the mean and standard deviation of the week of seroconversion for each group were calculated.

A repeated-measures analysis of variance (ANOVA) was used to compare between-group titers or differences in regard to number of pups that had seroconverted at the time of each vaccination, using Tukey's multiple comparison test. A values of p less than 0.05 were considered significant. All analyses were performed with computer software package SAS (version 8.1 for Windows).

Results

Change of maternal antibodies

To observe the declining pattern of maternal antibodies of pups against CPV, the 7 pups ingested dam's milk were examined for 17 weeks after birth. At one week of age, the geometric mean HI titer of maternal antibodies of pups against CPV was 641.4±271.3. The maternal antibody was declined gradually to 48.8±18.2 at 6 weeks of age, which was under the protective level(Fig 1).

Comparison of seroconversion rate of pups by four commercial combination vaccines

The geometric mean HI titer against CPV prior to the first vaccination at six weeks of age (i.e., maternally derived antibody titer) was 44.4±28.5 (range, 0 to 320), 47.3±34.9 (range, 0 to 320), 32.2±18.8 (range, 0 to 80), and 69.9±35.7 (range, 40 to 160) in vaccine C, G, K, and V group, respectively.

All of 20 pups vaccinated with vaccine V seroconverted by 15 weeks of age. Ten (50.0%) seroconverted after the first vaccination, nine (45.0%) seroconverted after the second vaccination, and one (5.0%) seroconverted after the third vaccination (Fig 2). However, 17 (94.6%) out of 18 pups vaccinated with vaccine C seroconverted by 15 weeks of age. Six (33.3%) seroconverted after the first vaccination, five (27.8%) seroconverted after the second vaccination, and six (33.3%) seroconverted after the third vaccination. Similarly, 16 (88.9%) out of 18 pups vaccinated with vaccine G seroconverted by 15 weeks of age. Four (22.2%) seroconverted after the first vaccination, ten (55.6%) seroconverted after the second vaccination, and two (11.1%) seroconverted after the third vaccination. And 16 (94.1%) out of 17 pups vaccinated with vaccine K seroconverted by 15 weeks of age. One (5.9%) seroconverted after the first vaccination, thirteen (76.5%) seroconverted after the second vaccination, and two (11.8%) seroconverted after the third vaccination. The seroconversion rate after the first and second vaccination of vaccine V group was significantly higher than those of vaccine C, G, and K groups ($p < 0.05$). However, the differences of seroconversion rate after third vaccination among all vaccination groups were not significant.

The geometric mean HI titer against CPV of pups vaccinated with vaccine V was increased sharply after the second vaccination, however those of pups vaccinated with vaccine C, G, and K were increased slightly. The geometric mean HI titer against CPV for pups in vaccine V group was significantly higher than those for pups in vaccine C, G, and K groups at 3 weeks after third vaccination ($p < 0.05$) (Fig 3). The geometric mean titer peaked at 3 weeks after third vaccination for pups in all vaccine groups. Although pups were vaccinated at 6 weeks of age, the geometric mean HI titer against CPV of pups in vaccine C, G, and K groups by 9 weeks of age were under the protective level.

Comparison of seroconversion rate of pups by three different vaccination schedules

The geometric mean HI titer against CPV prior to the first

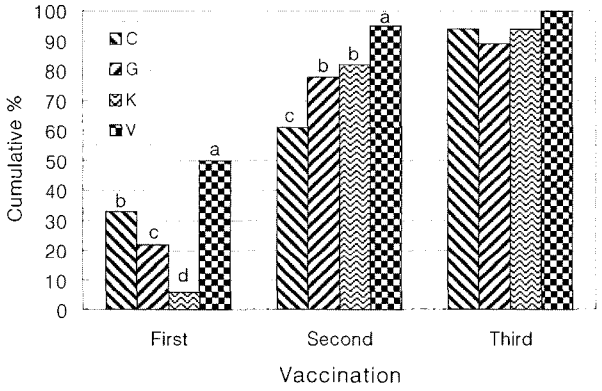

Fig 2. Cumulative percentages of pups that seroconverted, determined on the basis of serum hemagglutination inhibition titiers against canine parvovirus. All pups were vaccinated at six, nine, and 12 weeks of age with C, G, K, and V vaccines. Different letter over the each bar indicates that cumulative percentage is different significantly ($p<0.05$).

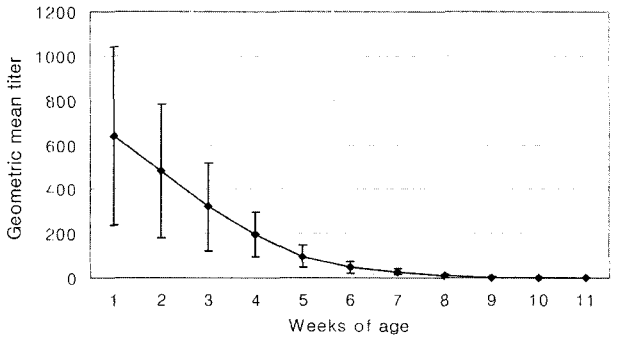

Fig 1. The change of geometric mean hemagglutination inhibition titer of maternal antibodies against canine parvovirus of 7 pups during 17 weeks after birth.

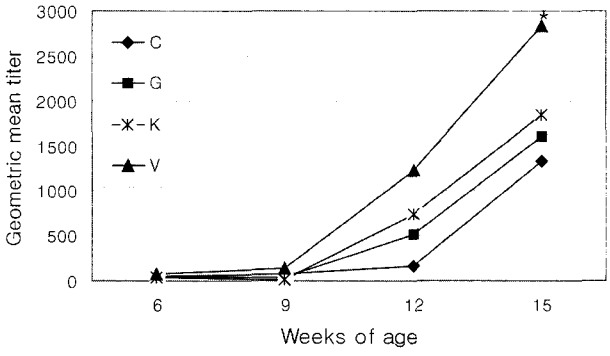

Fig 3. The changes of geometric mean hemagglutination inhibition (HI) titers against canine parvovirus of pups in four vaccine groups. HI titer of vaccine V group at 15 weeks of age was significantly higher than those of vaccine C, G, and K groups ($p< 0.05$).

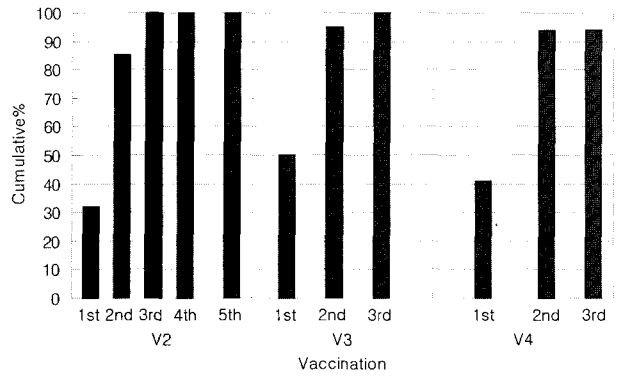

Fig 4. Cumulative percentages of pups that seroconverted, determined on the basis of serum hemagglutination inhibition titiers against canine parvovirus, after vaccination with vaccine V at different weeks of age, interval and frequency according to protocol of Table 1.

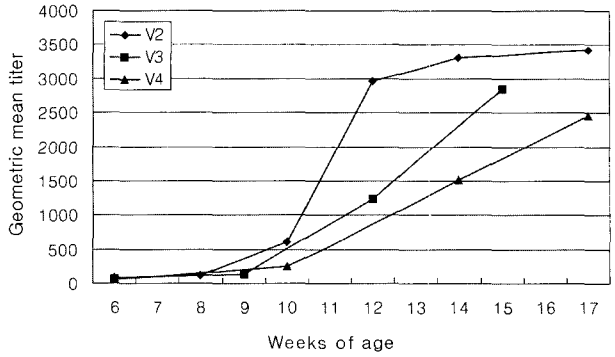

Fig 5. The changes of serum hemagglutination inhibition titers against canine parvovirus in pups after vaccination with vaccine V at different weeks of age, interval and frequency according to protocol of Table 1.

vaccination at six weeks of age (i.e., maternally derived antibody titer) was 86.1±42.3 (range, 40 to 160), 69.6±35.7 (range, 40 to 160), and 57.7±20.4 (range, 10 to 160) for pups in vaccine V2, V3, and V4 group, respectively.

All of 19 pups of V2 group seroconverted by 17 weeks of age. Six pups (31.6%) seroconverted after the first vaccination, ten (52.6%) seroconverted after the second vaccination, three (15.8%) seroconverted after the third vaccination (Fig 4). Similarly, all of 20 pups of V3 group seroconverted by 15 weeks of age. Ten (50.0%) seroconverted after the first vaccination, nine (45.0%) seroconverted after the second vaccination, and one (5.0%) seroconverted after the third vaccination. However, sixteen pups (94.1%) of V4 group seroconverted by 17 weeks of age. Seven (41.2%) seroconverted after the first vaccination, and nine (52.9%) seroconverted after the second vaccination. The remaining one pup (5.9%) did not seroconverted after the third vaccination.

The geometric mean HI titer against CPV of pups in all three groups (V2, V3, and V4 group) were increased sharply after 10 weeks of age. However, The geometric mean HI titer against CPV in V2 group was increased rapidly and higher than those in V3 and V4 groups (Fig 5).

Discussion

Neonatal pups are protected from CPV infection mainly by passive transfer of maternal antibodies. As maternal antibody titer declines, however, the pups become susceptible to infection. This decline in maternal antibody titer often coincides with the time that pups are separated from their dams[21], which increase the risk of being exposed to the virus and becoming infected. Therefore, use of a vaccine that protects pups earlier after vaccination should decrease the number of pups that become infected with CPV. However, response to vaccines will not occur until maternally derived antibodies have declined[11,21]. In the case of CPV, the level of matenal antibody that prevents adequate response to vaccines is lower than that required to prevent natural disease, which leaves nearly all pups susceptible to natural infection for a period of time[3,24]. This refractory period may depend on the amount of antibody transferred to the neonate and the half-life of the immunogloblins involved[27]. On the average, the level of passively acquired antibodies to CPV in puppies will have declined to insignificant levels by about 10 to 12 weeks, although in extreme cases they may persist for as long as 16 to 20 weeks. Therefore, investigating how maternal antibody concentration in dogs in the field setting relates to the age at which most pups are vaccinated is essential for the development a vaccination protocol[27]. In this study, the maternal antibodies of pups against CPV were declined to under the protective level at 6 weeks of age. The time declined to under the protective level was earlier than those of other study results[21,27]. And it was considered that vaccination of pups for CPV in Korea should be started at 6 weeks of age.

The immunogenicity and serological response to the CPV components or a combination vaccine depend on the virulence of the parent viral strain, the method and level of virus attenuation, and the amount of attenuated virus in each dose of vaccine. Development of new-generation, high-titer, low-passage CPV vaccines has overcome problems associated with maternal antibody interference to some extent[9,15]. However, differences in efficacy still exist. In this study the most of pups in four vaccine groups seroconverted to CPV after vaccination. However, after the first and second vaccination, the seroconversion rate of pups in vaccine V group was significantly higher than those of pups in vaccine C, G, and K groups. In addition, pups in vaccine V group seroconverted earlier than pups in vaccine C, G, and K groups regardless of HI titers. Thus, results of this study suggest that pups vaccinated with vaccine V would be protected earlier than pups vaccinated with other vaccines.

Maternally derived CPV HI titers of 1:80 or greater was considered to protect pups from infection, but titers between 1:10 and 1:80 are not protective and may interfere with vac-

cination, particularly when killed virus or low-titer modified-live virus vaccines are used[2,5,21]. In this study, the author used pups with a wide range of maternal HI antibody titer, including some pups with titers of 1:80 or greater. There were some pups in vaccine C, G, and K groups which were not seroconverted by 15 weeks of age. However, all pups vaccinated with V vaccine had seroconverted by 15 weeks of age, indicating that V vaccine was able to overcome interference by maternal antibodies. It is generally accepted that maternal antibody interference is responsible for a large portion of vaccine failures[27]. And improper handling of the vaccine (for example, vaccine stored too cold, too warm or for too long) is probably the another cause of vaccine failure 3. This could explain the lack of antibody titers in some of the vaccinated dogs.

A series of vaccinations is recommended to protect the pup at as young an age as possible[25,27]. Inactivated vaccines that produce weak immunity may require frequent administration. Maternal antibody interference can be prolonged, therefore, vaccination at six, nine, 12, 15, and 18 weeks of age has been recommended[11]. This schedule leaves a pup susceptible for an extended period, is expensive, and some owners may not obtain all the vaccinations. After high-titer vaccines are available, vaccination schedules have been changed so that most puppies receive their last dose of CPV vaccine at 12 weeks of age[12,26]. However, some manufactures of commercial high-titer vaccines still recommend that pups should be vaccinated until they are 16 weeks of age or older. In this study, The geometric mean HI titer against CPV of pups which were vaccinated with V vaccine at 2 weeks interval was increased rapidly and higher than those of pups which were vaccinated at 3 weeks or 4 weeks interval. However, vaccination at 3 weeks interval induced sufficient immune response.

The immunogenicity and serological response to the CPV component of a combination vaccine depend on the virulence of the parent viral strain, the method and level of virus attenuation, and the amount of attenuated virus in each dose of vaccine. Coyne[6] reported that the CPV component did not appear to interfere with response to the CDV component. However, there is no evidence in the literature that the parainfluenza, adenovirus, or *Leptospira* components alter the serological response to CPV component in combination vaccines.

In conclusion, the immunogenicity of V vaccine was superior to the other vaccines, and optimum vaccination schedule was 3 times vaccination with 3 weeks-interval starting vaccination at 6 weeks of age when the combination vaccine was used.

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Canine parvovirus 함유 혼합백신들과 예방접종 스케줄에 따른 강아지의 혈청학적 반응

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요 약 : 본 연구에서는 우리나라 실정에 맞는 개 파보바이러스 백신의 예방접종 프로토콜을 마련하기 위하여, 국내에서 사용 중인 4종류의 상업용 백신과 3가지의 예방접종 스케줄에 따른 면역형성 능력을 비교 평가하였다. 생후 6주령에 예방접종을 실시하기 위하여 동물병원에 내원한 120두의 강아지를 4종류의 백신[C, G, K, V(또는 V3) 접종군]과 예방접종 스케줄[V2, V3, V4 접종군]에 따라 20두씩 임의배치하였다. 그리고 모체이행 항체의 소장상태를 확인하기 위하여 동복의 건강한 7마리의 강아지를 예방접종을 실시하지 않고 17주 동안 관찰하였다. C, G, K, V(또는 V3) 접종군은 3주 간격으로 3회(6, 9, 12주), V2군은 5회(6, 8, 10, 12, 14주), V4군은 3회(6, 10, 14주)에 피하로 예방접종을 실시하였다. 혈액은 생후 6주에 처음 채취하고 매 추가접종을 실시할 때와 마지막 예방접종을 실시한 후 3주 후에 한 번 더 채취하였으며 개 파보바이러스에 대한 혈청 혈구응집억제 항체가를 측정하였다. Seroconversion(혈청변환)은 전번의 항체가보다 4배 이상 증가하는 것으로 정의하였다. 파보바이러스에 대한 강아지의 모체이행항체는 6주령에 방어수준 이하로 떨어졌으며 개 파보바이러스에 대한 예방접종은 6주령에 시작하여야 할 것으로 생각되었다. 백신에 따른 면역형성능에서 V 백신의 면역형성 능력이 다른 백신보다 우수하였으며 백신 종류에 따라 면역형성 능력에 차이가 인정되므로 사용되는 백신의 효능을 주기적으로 평가하여야 할 것으로 판단되었다. 그리고 혼합백신을 사용하는 경우 예방접종 스케줄은 6주령에 예방접종을 시작하여 3주 간격으로 3회 접종하는 것이 합리적인 것으로 판단되었다. 그러나 예방접종을 실시한 모든 군의 대부분의 강아지는 생후 9주령까지 항체가 수준이 방어수준 이하로 나타나 개 파보바이러스의 감염을 예방하기 위하여 이 시기까지는 감염위험성이 높은 곳에 노출되는 것을 피해야 할 것으로 생각되었다.

주요어 : 개 파보바이러스, 백신, 백신접종 스케줄, 혈구응집억제 항체가