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Journal of Veterinary Medicine and Research

Research Article

Comparison of Vaccination Protocols for Bovine Herpesvirus Type1 and Bovine Viral Diarrhea Virus

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Submitted: 22 May 2015

Accepted: 30 September 2015

Published: 01 October 2015

ISSN: 2378-931X

Keywords

- Bovine herpes virus type 1
- Bovine viral diarrhea virus
- Vaccination

Abstract

We investigated the immune responses against bovine herpesvirus type 1 (BHV-1) and bovine viral diarrhea virus (BVDV) by two different vaccination protocols. An attenuated-live vaccine (containing BHV-1 and BVDV-1) and an inactivated vaccine (containing inactivated virus antigens of BHV-1, BVDV-1, and BVDV-2) were used. Two different immunization protocols were investigated: inoculation of live vaccine 28 days after inactivated vaccine inoculation (KL), and inoculation of inactivated vaccine 28 days after live vaccine inoculation (LK). Antibodies against BHV-1, BVDV-1, and BVDV-2 were examined. Antibody titer against BHV-1 was significantly higher in calves vaccinated by the KL protocol 30 days post inoculation (dpi). On the other hand, antibody titer against BVDV-1 was significantly lower in calves vaccinated by the KL protocol 30 dpi. However, approximately equivalent antibody titers were observed using either protocol by 56 dpi. No significant difference in antibody titer against BVDV-2 was observed between the two protocols, with a nearly equivalent immune response acquired by 56 dpi. These results suggest that when combination vaccines are used, the vaccination protocol should be selected depending on the prevalence of infectious diseases in each farm.

ABBREVIATIONS

BHV-1: Bovine Herpesvirus Type 1; BVDV: Bovine Viral Diarrhea Virus; Dpi: Days Post Inoculation; KL: Killed-Lived; LK: Live-Killed

INTRODUCTION

Eradication of bovine herpesvirus type 1 (BHV-1) and bovine viral diarrhea virus (BVDV) is being continuously pursued in many countries [1,2], and vaccinations are widely utilized to control these viral infectious diseases [3]. Vaccines against both viruses are commercially available as a single combination vaccine in Japan. Because both viruses are important pathogens involved in the bovine respiratory disease complex, combinatorial control of infection is usually performed due to superior cost and efficiency [3, 4], for example combination vaccine can be induced immune responses against some pathogens by only one injection.

Both modified live-attenuated and inactivated BHV-1 and BVDV vaccines are currently available on the market. In general, modified live-attenuated vaccines induce high levels of serum-neutralizing antibodies with a single inoculation and can maintain a high antibody titer. This prolonged immune reaction induced by live-attenuated vaccines is thought to replicate the vaccine strain virus in the animal [5, 6]. However, calves are unable to produce an immune response to vaccination with the presence of colostral maternal antibodies, or if in a stressed state [7, 8]. Therefore, additional inoculation is recommended for calves aged 6 months or under to bolster immunization [9]. In Japan, the modified-live-killed (LK) vaccination protocol, in which an inactivated vaccine is inoculated after a modified-live vaccine inoculation, is most commonly used for bovine respiratory problems in pasture [9]. It has been reported that the killed-live (KL) vaccination protocol for BVDV, in which modified-live BVDV-1 vaccine is inoculated after inactivated BVDV-1 vaccine inoculation, is effective against a broader spectrum of viral antigenicity, including BVDV-1 and -2 [10]. In Japan, there are no vaccines available only against BVDV. It remains unclear which two-step combinatorial vaccination system, LK or KL, provides superior immunization. In the present study, efficacy of the LK and KL vaccination protocols using combination vaccines were investigated by serial measurement of antibody titer after immunization.

MATERIALS AND METHODS

Experimental animals

Ten 3- or 4-month-old female Holstein calves were used in this study. All calves had been given 4 L of colostrum by stomach tube within 4 h of birth, and individually fed in a calf hutch at our farm. The calves were not exposed to calves or cows from other farms. There were approximately 400 adult cows, including 300 milking cows and 100 heifers, and 50 calves, present at our farm during the study, with no introduction of new cows to the farm in the 11 years prior to the start of the present study. All cows were born in the present farm and vaccinated when 3-months-old or older using attenuated-live vaccine against BHV-1 and BVDV-1. Except for the 10 present experimental calves, all cows were inoculated using live vaccine. The 10 calves were almost the same birthday. They were fed under the same natural conditions such as environment, climate, and food and so on during the observation period. This study was conducted according to the guidelines of the Experimental Animal Research Committee of Rakuno Gakuen University.

Vaccination protocol

Five 4-month-old calves were inoculated with a multivalent inactivated vaccine containing BHV-1, BVDV-1 and BVDV-2 antigens (adjuvant added; Stockguard 5, Pfizer Japan Inc. (Zoetis Japan Inc.), Tokyo). Twenty-eight days after initial inoculation (when 5 months old), the calves were inoculated with a multivalent live vaccine containing attenuated BHV-1 and BVDV-1 (IBR, BVD-MD (mucosal disease), BRSV, PI, AD live vaccine, Kyoto Biken Laboratories, Inc., Kyoto, Japan). This vaccination protocol was defined as the KL protocol. The remaining 5 calves were first inoculated with live vaccine when 3 months old, and again with the inactivated vaccine 28 days later. This vaccination protocol was defined as the LK protocol. All calves were inoculated with their respective vaccines on the same day.

Measurement of neutralizing antibody titer

Blood was collected from the calves before the first vaccine inoculation (Day 0), and 28, 30, 35, 56 and 78 days post inoculation (dpi) of the first vaccine. Serum was separated from the blood and stored at a temperature less than -20°C until use. Neutralizing antibody titer was measured by a 96-well plate serial dilution protocol. 200 x TCID50 in 100μL of BHV-1 (strain No. 758), BVDV-1 (strain Nose), and BVDV-2 (strain KZ91cp) were used as viruses for neutralization. Viral neutralizing tests were performed by Kyoto Biken Laboratories Inc... The neutralizing antibody titer was calculated by obtaining the maximum serial serum dilution at which inhibition of cytopathic effects was observed. Antibody titers were analyzed statistically by Student's t-test. $p<0.05$ was considered significant.

RESULTS

Immune response against BHV-1

The changes of antibody titers against BHV-1 were almost the same in both vaccination methods. The KL protocol induced a higher antibody titer than the LK protocol till 56 dpi (Figure 1). At 30 dpi, antibody titer by the KL protocol was significantly higher ($p<0.01$) than that by the LK protocol. In both protocols, antibodies against BHV-1 were not induced sufficiently by the first inoculation; however, the response against BHV-1 was faster by the KL protocol than the LK protocol. After 56 dpi, no difference in antibody titer could be observed between the two protocols.

Immune response against BVDV

Antibodies against BVDV-1 were significantly higher ($p<0.01$) at 28, 30 and 35 dpi in calves vaccinated by the LK protocol than in those by the KL protocol (Figure 2). However, changes in antibody titer against BVDV-2 were approximately the same in both protocols (Figure 3). The appearance of the changes of antibody titers against BVDV-2 was almost the same with that against BHV-1. The increase in antibodies against both BVDV-1 and -2 was slower in calves vaccinated by the KL protocol. After 56 dpi, antibody titers were approximately the same (about 32) in calves vaccinated by either protocol.

Clinical manifestations

All experimental caves in the present study were apparently healthy throughout the observation period. No abnormal vital data were noted on any of the blood sample collection days (data

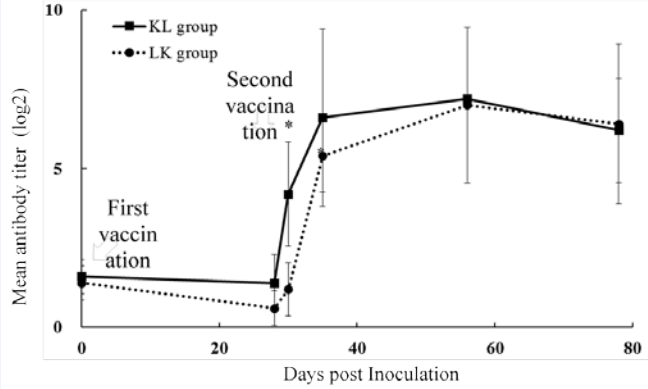

Figure 1 Antibody titer against BHV-1 Arrows indicate the day of vaccination. The KL and LK protocols were described in Materials and Methods. *: Significant difference between protocols at respective dpi (days post inoculation of first vaccination).

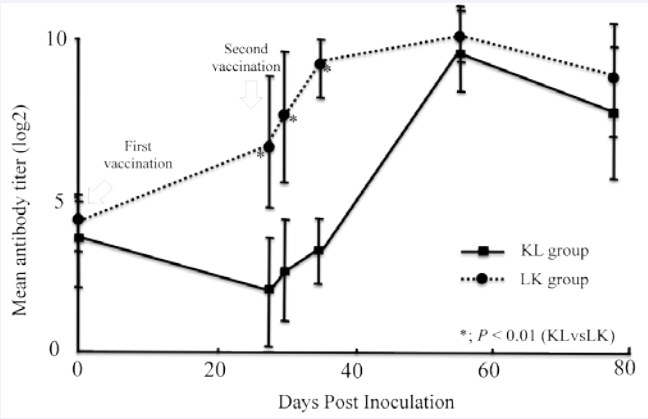

Figure 2 Antibody titer against BVDV-1.

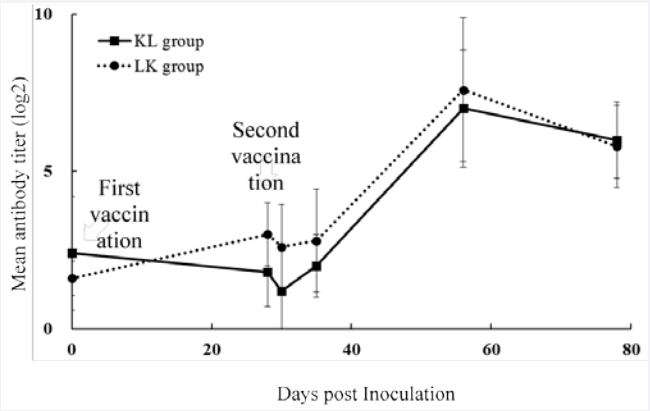

Figure 3 Antibody titer against BVDV-2.

not shown). These data indicated that there were no obvious side effects or adverse effects by the combinatorial use of the two types of vaccines.

DISCUSSION

In the present study, we investigated the efficacy of two vaccination protocols for bovine viral respiratory disease using either modified-live or inactivated multivalent combination vaccines, and observing antibody production response. The LK protocol induced higher levels of BVDV antibody titer than the KL protocol. Although final antibody response against BHV-1 was approximately the same using either vaccination protocol, antibody titer in the LK protocol was higher till 56 dpi. BHV-1, BVDV-1 and -2 antibody titers were approximately equivalent using either protocol by 78 dpi. In Japan, bovine vaccines for respiratory diseases are available only as combination vaccines. The results of the present study suggest that the vaccination protocol should be considered depending on the prevalence of pathogens in each farm or area.

Moennig et al. [10] demonstrated that priming with inactivated vaccine reduced or even prevented viraemia after booster vaccination using the attenuated vaccine, therefore reducing or preventing shedding of the vaccine virus. Thus, the authors recommended the KL protocol for BVDV vaccination. In the present study, antibody responses in the KL protocol were inferior to those in the LK protocol, as shown in Fig. 2. However, because the final antibody titers were not significantly different between the vaccinations protocols, either protocol may be sufficient for immunization.

Generally, higher immune responses are induced by modified-live vaccines. In the present study, antibody titers against BHV-1 were elevated after the second vaccination, independent of vaccination protocol. In the LK protocol, antibody response against BHV-1 was not induced after the first vaccination using the modified-live vaccine. This may be possibly due to the presence of remaining maternal antibodies. All calves in the present study had neutralizing antibodies against BHV-1 of 2 to 8 and BVDV of 2 to 32 titers. It has been previously reported that presence of maternal antibodies against BVDV was able to neutralize virus up to 64 titer in the calf immune system [11]. As shown in Figure 2, antibody response against BVDV modified-live vaccine can be seen clearly. These results correspond well with a previous study reporting that immunity by live vaccine was achieved rapidly after administration of a single dose (within 7 to 10 days) [12].

The live vaccine used in the present study did not contain a BVDV-2 strain. In both vaccination protocols, an increase in titer of antibody against BVDV-2 was observed 28 days after the second vaccination (56 dpi). These antibodies may have originated from a cross-reaction with BVDV-1, which was included in the live vaccine. Moennig et al. [10] reported that protection against fetal BVDV-2 infection could be extended with a two-step KL protocol than with a single dose of live vaccine, and that a wide spectrum of cross immunity could be obtained. Interestingly, the inactivated vaccine used in the present study included BVDV-2 antigen, however, the antibody response against BVDV-2 was not as pronounced as it was against BHV-1 and BVDV-1. Therefore, to investigate which protocol is superior for sufficient immunization of BVDV-2, comparison of the diversity in antibody titer between the LK and KL protocols using BVDV-2 live-vaccine may be needed.

Antibody responses to BHV-1 and BVDV vaccines were compared by changing the order of inoculation of modified-live and inactivated vaccines in the presence of maternal antibodies. However, maternal antibodies may have had a minor impact on T-cell response to BVDV [13]. A more detailed investigation examining T-cell activation may be required to compare the efficiency of the KL and LK protocols.

In conclusion, both LK and KL protocol can be immunized sufficiently; however, the rising time of antibody titer was different. When combination vaccines are used, the vaccination protocol should be selected depending on the prevalence of infectious disease in each farm.

ACKNOWLEDGMENT

The authors express our special thanks to Kyoto Biken Laboratories for their kind assistance in performing antibody titration by the virus neutralization test.

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Cite this article

Kato H, Sato R, Oonishi M, Tajima M (2015) Comparison of Vaccination Protocols for Bovine Herpesvirus Type1 and Bovine Viral Diarrhea Virus. J Vet Med Res 2(5): 1034.