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Effects of injectable trace minerals administered concurrently with a modified live virus vaccine on long-term protection against bovine viral diarrhea virus acute infection in dairy calves

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ABSTRACT

The objective was to evaluate the effects of injectable trace minerals (ITM) concurrent with modified-live virus (MLV) vaccination on protection from bovine viral diarrhea virus (BVDV) infection in dairy calves. In a previous study (Palomares et al., 2016), thirty dairy calves received two doses of a MLV vaccine subcutaneously (SC), concurrently with ITM ($n = 15$) or saline (n = 15), SC. Five months later, 20 of these calves received ITM (G1, $n = 10$) or saline (G2, n = 10) according to their previous groups and were challenged intranasally with BVDV2. Five unvaccinated calves were also challenged with BVDV2 (G3). Blood samples were collected on days 0 (BVDV challenge), 3, 5, 6, 7, 8, 9, 11, 14, 18, 21, 32 and 61 for leukocyte count, virus isolation and BVDV serum neutralizing antibodies (SNA). Mild-moderate clinical signs were observed in G3 after BVDV challenge. Group 1 showed lower sum health score and nasal score on d5 and fecal score on d8 compared to G2. Rectal temperature and leukocyte counts were not different between G1 and G2. In contrast, G3 calves had significant leukopenia and lymphopenia from d3 to d7 ($P < .05$) and higher rectal temperatures on d6 to d8, compared to values on d0 ($P < .05$). All unvaccinated calves became viremic, while viremia was not detected in G1 or G2. Average daily gain was not different between vaccinated groups, however, only G1 calves had significantly greater ($P = .04$) ADG compared to non-vaccinated calves during the first 14 days post challenge. Vaccinated calves treated or not with ITM were protected from BVDV2 infection five months post-vaccination.

1. Introduction

Bovine respiratory disease complex (BRDC) is one of the most important health issues of young livestock in the United States (USDA APHIS. Dairy Heifer Raiser, 2011). Moreover, BRDC was the second most common disease in pre-weaned dairy heifers and also a major illness affecting weaned dairy heifers. Prevalence of BRDC has been reported to be almost 6 times higher than all other common diseases affecting post-weaned heifers (digestive problems, lameness/injury and navel infection; USDA APHIS. Dairy Heifer Raiser, 2011). The pathogens most commonly involved in BRDC include bovine viral diarrhea virus (BVDV), bovine herpes virus 1 (BHV1), bovine respiratory syncytial virus (BRSV), parainfluenza 3 virus (PI3V), *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*. Bovine viral diarrhea virus is known to cause immunosuppression potentiating infection by other pathogens (e.g. *Pasteurella multocida* and *Mannheimia haemolytica*), which contributes to disease severity. Cattle persistently infected with BVDV are the main source of BVDV transmission in domestic cattle, and play an important role in the dissemination and pathogenesis of BVDV (Moennig and Becher, 2015). Intensive efforts have been made to reduce the incidence BVDV acute infections and to eliminate persistent infections among cattle populations.

Vaccination is a powerful tool to prevent BVDV infections, and

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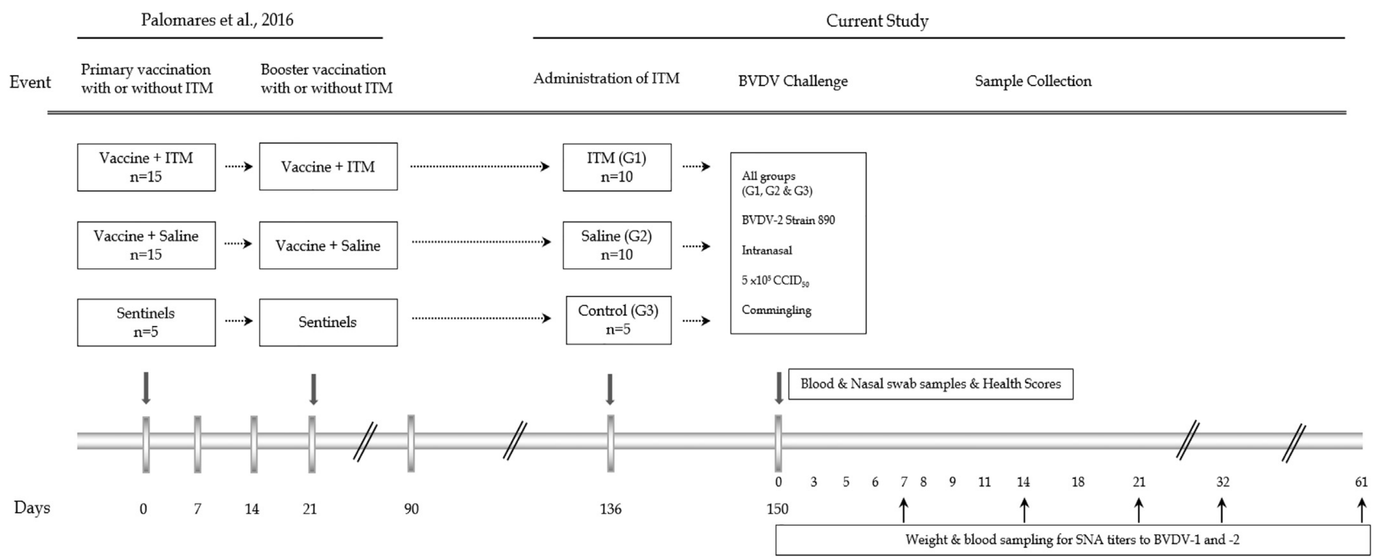

Fig. 1. Experimental design of the previous study (Palomares et al., 2016) administering injectable trace minerals (ITM) or saline concurrent with BRDC-MLV vaccination in dairy calves (at 3.5 months of age and 21 days later); and the current study administering another dose of ITM or saline 14 days before BVDV-2 challenge (approximately at 8 months of age).

modified-live virus (MLV) vaccines have the benefit of stimulating both arms of the immune system (antibody production and cell mediated immunity) enhancing all the means for the control of virus replication, viremia and shedding (Rhodes et al., 1999). Nonetheless, even with the extensive use of both inactivated and live attenuated vaccines to manage BVDV, cattle can succumb to disease (Fulton et al., 2005a; Kelling et al., 2005). Factors such as interference by transferred maternal antibodies in calves < 60 days of age (Ellis et al., 2001; Chamorro et al., 2015), the general immunological status of cattle, weather stress, antigenic mismatch between different vaccine and field viruses, vaccine handling, and level of pathogen exposure, have been documented to affect the immune response and protection after vaccination (Heininger et al., 2012). Nutritional deficiencies may also contribute to poor vaccine response in cattle (Rice et al., 1986; Thomas, 2009).

Several studies have demonstrated the impact of trace minerals on cattle health and performance (Enjalbert et al., 2006; Galyean et al., 1999; Underwood and Suttle, 1999). Trace minerals such as zinc (Zn), manganese (Mn), copper (Cu), and selenium (Se) are essential for optimal immune function (Chirase et al., 1994; Percival, 1998; Underwood and Suttle, 1999), health status and growth in cattle (Spears and Kegley, 2002), particularly in highly stressed cattle, such as newly received feeder calves (Duff and Galyean, 2007).

Multiple factors affect trace minerals levels in cattle, including high variability in requirements and mineral intake among cattle accordingly to their production stage, inadequate trace mineral levels in soil, forages, and feedstuffs, as well as the presence of mineral antagonists in feed, water, and forages, which limit their absorption. The use of injectable trace minerals (ITM) has advantages such as delivery of a known and controlled amount of mineral and rapid and efficient absorption and storage following treatment (Pogge et al., 2012). This might be relevant for cattle having reduced dry matter intake (i.e. during transportation and receiving periods, weaning and vaccination). Thus, the use of ITM reduces the variability in trace minerals levels observed in most cattle given free choice mineral intake (Arthington and Swenson, 2004).

Previous studies have shown positive effects of ITM administration on humoral and cell mediated immune response to BRDC vaccines in dairy (Palomares et al., 2016; Bittar et al., 2018) and beef cattle (Arthington and Havenga, 2012; Roberts et al., 2016; Bittar et al., 2016). We previously demonstrated that the use of ITM concurrently with a BRDC-MLV vaccine in dairy calves resulted in earlier and more robust antibody titers to BVDV1, and stronger mononuclear cell proliferation after stimulation with BVDV1 and BRSV antigen than the control calves (Palomares et al., 2016). Additionally, ITM enhanced antibody titers to *Mannheimia haemolytica* and proliferation of mononuclear cells after *Pasteurella multocida* stimulation (Bittar et al., 2018).

Given the available data indicating that ITM can impact immune responses to vaccination, studies to determine the efficacy of the concomitant use of ITM with MLV vaccines on protection against pathogens involved in the BRDC are warranted. In the present study, we hypothesized that administration of ITM at the time of MLV vaccination and again 5 months later improves the immune response and long-term protection against experimental BVDV2 acute infection in dairy bull calves. Therefore, our objective was to assess the effects of injectable trace minerals supplementation (containing Cu, Zn, Mn and Se) used concurrently with a BRDC-MLV vaccine, and again 5 months later, on the humoral immune response and protection from a non-cytopathic (ncp) BVDV2 experimental infection five months after priming vaccination in dairy bull calves.

2. Materials and methods

2.1. Experimental design, vaccination, and treatments

The study was performed at the University of Georgia (UGA) Oconee Farm (Watkinsville-GA) from October 2014 through January 2015. The research protocol was conducted as approved by the University of Georgia, Institutional Animal Care and Use Committee (UGA-IACUC# A201402-005-Y2-A5). This study was performed using 25 weaned intact Holstein bull calves (from the commercial farm BrooksCo Dairy, Quitman GA) that were previously used in another study (Palomares et al., 2016). The experimental design of the previously reported study (Palomares et al., 2016) and the current trial are shown in Fig. 1. The animals averaged eight months of age at enrolment. During the study, calves grazed fescue grass (*Festuca arundinacea*) with free access to Bermuda grass hay (*Cynodon dactylon*), and water ad libitum. In addition, calves received daily supplementation (2.5 Kgs per calf) of a commercial ration (Cattleman's special beef; Godfreys Warehouse; Madison-GA) offered in two meals. No additional mineral supplementation was provided.

In the previous study, an initial group of thirty calves (3.5 months of