Effect of vaccination against foot-and-mouth disease on growth performance of Korean native goat (Capra hircus coreanae)1

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ABSTRACT: The objectives of this study were 1) to evaluate the effects of vaccination against foot-and-mouth disease (FMD) on growth performance, nutrient digestibility, hematological parameters, and behavior in a ruminant animal and 2) to investigate a possible strategy for reducing its adverse effect. A total of 12 Korean native goats (Capra hircus coreanae; 19.8 ± 2.9 kg) were used in a crossover design with 3 experimental periods and 3 treatments, randomized and balanced for counteracting possible carry-over effects. The treatments were 1) control, 2) co-injection with a commercially available dipyrone (CADI), and 3) supplementation with γ-amino butyric acid (GABA) at 10 g/kg in concentrate mix. Each period lasted 4 wk, and the vaccination against FMD was performed at 2 wk after the start of each period. The goats were individually housed in a metabolic cage and fed ad libitum with a diet consisting of bermuda grass and commercial concentrate mix (6:4, wt/wt). Dry matter intake, ADG, nutrients digestibility, hematological parameters, and behavioral activities of the goats were measured before and after vaccination. Although DMI was not decreased (P > 0.05), ADG was decreased by the vaccination to the goats (P < 0.01). The total number of leukocytes was increased while that of erythrocytes was decreased by the FMD vaccination (P < 0.01). The vaccination shortened standing time while extended lying time and the time spent in drinking (P < 0.05). The treatment by CADI reduced the adverse effect of vaccination on ADG and goat behavior compared with control and GABA treatment (P < 0.05).

We concluded that the FMD vaccination decreased ADG of the goats without depression of diet intake, and CADI may attenuate the adverse effect of the FMD vaccination.

Key words: foot-and-mouth disease, Korean native goat (Capra hircus coreanae), stress attenuation


INTRODUCTION

Foot-and-mouth disease (FMD), which occurs in hoofed and even-toed livestock animals, is a highly contagious viral disease, and infected or suspected animals are often culled to prevent further spread of the disease. However, culling was insufficient under certain circumstances as seen in the Netherlands and Japan FMD outbreaks in 2001 and 2010 (Paton and Taylor, 2011), and vaccination is a powerful tool for the control of this disease (Golde et al., 2005; Tildesley et al., 2006).

The vaccination practice, however, can be a stressful management practice to the animal due to the act of handling of the animals, the injection, or a possible inflammatory response, and some adverse effects caused by the use of vaccination have been reported. Growth reduction, disturbance of pregnancy, and drop in milk production by vaccination were observed in various species (Yeruham et al., 2001).

Therefore, a strategy is needed to attenuate the side effects of the FMD vaccination, and a possible strategy is to supplement or inject nonsteroidal anti-inflammatory drugs (NSAID) or γ-aminobutyric acid (GABA; Bebbehani et al., 1990; Kehlet and Holte, 2001). Gilron et al. (2006) reported that NSAID was usually effective in possible neuropathic pain and inflammatory response. Previous studies showed positive effects of NSAID (i.e., ketoprofen and meloxicam) on pain or painful interventions in ruminants (Ting et al., 2003a; Stafford and Mellor, 2011; Coetzee et al., 2012). Gabapentin, an

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analogue of GABA, was also used to reduce neuropathic pain in a ruminant (Coetzee et al., 2011). Some studies have reported the positive effect of GABA on stress and performance of animals (Dai et al., 2011; Zhang et al., 2012; Xie et al., 2013).

Therefore, the aims of this study were 1) to evaluate the effects of FMD vaccination on growth performance, nutrient digestibility, hematological response, and animal behavior and 2) to investigate a possible strategy (i.e., injection of dipyrone and supplementation of GABA) for reducing its negative effects.

MATERIALS AND METHODS

This study was conducted at Center for Animal Science Research, Chungnam National University, Korea. Animal use and the protocols for this experiment were reviewed and preapproved by the Chungnam National University (CNU) Animal Research Ethics Committee (CNU-00072).

Animals and Diets

A total of 12 Korean native goats (Capra hircus coreanae) weighing 19.8 ± 2.9 kg and 8 mo of age were used for this study and were housed individually in a metabolic cage in an environmentally controlled animal research facility at Chungnam National University in Korea. The treatments of this study were 1) control (no treatment), 2) co-injection of commercially available dipyrone (CADI; 50 mg), and 3) supplementation with 10 g/kg of GABA in concentrate mix. The CADI and GABA were obtained from Samyang Anipharm Co. (Seoul, Korea) and Adbiotech (Chuncheon, Korea), respectively. Goats were fed with a diet consisting of bermuda grass and concentrate mix (6:4, wt/wt) formulated to meet nutrient requirements for indigenous goats according to NRC (2007). As the purity of commercially available GABA was 360 g/kg, the actual concentration of GABA in the diet was 1.4 g/kg of dietary DM. Feed ingredients and chemical composition of the diets are shown in Table 1. The goats had free access to drinking water throughout the experiment. The concentrate mix and forage was fed ad libitum twice daily (0900 and 1800 h). Individual daily feed intake was recorded by measuring feed offered and refusals.

Experimental Design

The experiment was performed using a crossover design with 3 periods and 3 treatments in which each of the 12 goats (the experimental units) were randomly allocated and received different treatment in each experimental period. Each experimental period lasted 4 wk divided into 4 stages: adaptation (1 wk), before vaccination (1 wk), after vaccination (1 wk), and wash-out week (1 wk; Fig. 1). To counteract possible carry-over effects, the wash-out week was included between 2 consecutive experimental periods, and the sequences of the treatments were randomized and balanced so that different animals were tested on every possible order of the treatments. The FMD vaccine (Decivac FMD DOE; Intervet/Schering-Plough Animal Health, Boxmeer, Netherlands) was stored at 4°C until use, and 1 mL of the FMD vaccine was administered intramuscularly behind the elbow according to the manufacturer’s protocol before the morning feeding on d 14 after the start of each period. The CADI group was injected with the mixture of FMD vaccine and CADI (10:1, vol/vol) following the manufacturer’s recommendation. During the wash-out week, all goats were fed with bermuda grass and the basal concentrate mix.

One of the goats was eliminated at the end of the first experimental period due to urinary calculi and was not replaced. Consequently the number of experimental units used for the data analysis is 11.

Table 1. Diet formulation and analyzed composition of the experimental diets

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Bermuda grass</th>
<th>Basal concentrate mix&lt;sup&gt;2&lt;/sup&gt;</th>
<th>GABA&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM, g/kg as fed</td>
<td>953.9</td>
<td>916.5</td>
<td>899.1</td>
</tr>
<tr>
<td>CP</td>
<td>73.3</td>
<td>152.5</td>
<td>161.7</td>
</tr>
<tr>
<td>EE&lt;sup&gt;4&lt;/sup&gt;</td>
<td>14.7</td>
<td>40.1</td>
<td>42.2</td>
</tr>
<tr>
<td>Ash</td>
<td>95.6</td>
<td>94.1</td>
<td>95.2</td>
</tr>
<tr>
<td>aNDF&lt;sup&gt;5&lt;/sup&gt;</td>
<td>756.5</td>
<td>408.5</td>
<td>410.1</td>
</tr>
<tr>
<td>ADF</td>
<td>505.9</td>
<td>304.8</td>
<td>329.5</td>
</tr>
</tbody>
</table>

<sup>1</sup> 33,330,000 IU/kg vitamin A, 40,000,000 IU/kg vitamin D, 20.86 IU/kg vitamin E, 20 mg/kg Cu, 90 mg/kg Mn, 100 mg/kg Zn, 250 mg/kg Fe, 0.4 mg/kg I, and 0.4 mg/kg Se.
<sup>2</sup> Experimental concentrate mix fed without supplementation of γ-aminobutyric acid (GABA).
<sup>3</sup> Experimental concentrate mix with supplementation of gamma-aminobutyric acid at 10 g/kg.
<sup>4</sup> EE = ether extract.
<sup>5</sup> aNDF = amylase-treated NDF.
Sample Collection

Body weight was measured weekly (0, 7, 14, and 21 d) before morning feeding throughout the experiment. Total residual feed, feces, and urine were collected for 3 consecutive days on 10 through 12 d (before vaccination) and on 19 through 21 d (after vaccination) to compare changes in nutrient digestibility and nitrogen utilization of goats by vaccination. Daily residual feed from each goat were collected, weighed, and then stored at 4°C until subsequent analysis. Using a metabolic cage with a sloping stainless steel bottom to collect urine and fitted with a stainless steel screen (5 mm mesh) under the floor of the cage, total urine and feces were separately collected without contamination. Fecal samples were weighed and dried at 60°C for 72 h for determination of DM content and then stored at room temperature until following chemical analysis. Urine, filtered through 4 layers of cheesecloth, was collected in a glass bottle containing 200 mL of 2.8% HCl to prevent ammonia volatilization. Subsample of collected urine was then stored at ~20°C until analysis for nitrogen. Blood samples were taken on the vaccination day (14 d) at 1.5 h before vaccination and 8 h after vaccination to assess changes in hematological response. Approximately 10 mL of blood was taken from the jugular vein of each goat and collected into a Vacutainer tube containing EDTA (Becton Dickinson Vacutainer Systems, Plymouth, UK). The tubes were placed on ice and then immediately transferred to the analytical laboratory of Animal Hospital at Chungnam National University for the complete blood count analysis.

Chemical Analysis

Daily samples of feed, orts, and feces from each goat were dried at 60°C for 72 h, ground to pass a 1-mm screen, and composited by sampling period before chemical analysis. Dry matter (number 934.01), CP (number 976.05), ash (number 942.05), ether extract (EE; number 920.39), and ADF (number 973.18) were determined as described by AOAC (2005). Crude protein was calculated as 6.25 times nitrogen content, and total nitrogen was measured using the Kjeldahl method using a DK 20 Heating Digester and Semi-Automatic Distillation Unit Model UDK 139 (VELP Scientifica, Usmate, Italy). The amount of amylase-treated NDF (aNDF) was determined with heat stable α-amylase and without sodium sulfite according to the method of Van Soest et al. (1991). Urine samples composited by sampling period for each animal were analyzed for total nitrogen using the Kjeldahl method (number 976.05) as described by AOAC (2005).

Behavioral Observation

To observe behavioral changes by vaccination, video was recorded for 9 h from morning feeding (0900 h) to evening feeding (1800 h) on 13 d (before vaccination) and 15 d (after vaccination) using 4 surveillance cameras (Ting et al., 2003b). The variation in behavior (standing, lying, eating, and drinking) was assessed by 1 person to avoid interobserver variation. The standing was defined as the sum of time taken in a standing posture with or without physical activity. The lying included total time spent in lying posture in the ventral or lateral position on the floor with resting and ruminating. The eating and the drinking were also visually assessed and summed.

Statistical Analysis

Data were analyzed with PROC MIXED (SAS Inst. Inc., Cary, NC). The potential carry-over effects by vaccination and/or treatment during each period were not significant in any tested variables as assessed by insignificant interactions between time period and either treatment or vaccination. This implied the response by the goats to the vaccination and treatment was consistent during each period, even though different animals received each treatment. The interaction terms between time period and other variables were therefore omitted for the statistical analysis. The linear model was as follows:
Effect of foot-and-mouth disease vaccination

Effect of foot-and-mouth disease vaccination

\[ y_{ijkl} = \mu + \alpha_i + b_j + \gamma_k + \tau_l + (\gamma \tau)_{kl} + \epsilon_{ijkl}, \]

in which \( y_{ijkl} \) is an observed dependent variable, \( \mu \) is overall mean, \( \alpha_i \) is the fixed effect of period, \( b_j \) is the random effect of animal, \( \gamma_k \) is the fixed effect of vaccination, \( \tau_l \) is the fixed effect of treatment, \( (\gamma \tau)_{ij} \) is the interaction between treatment and vaccination, and \( \epsilon_{ijkl} \) is unexplained error.

Pairwise comparisons of the least square means were conducted using the PDIFF option with Tukey-Kramer adjustment. Significance was declared at \( P < 0.05 \), and a trend was discussed at \( 0.05 \leq P < 0.1 \).

RESULTS

Intake and Growth Performance

Even though DMI was numerically declined after vaccination, no significant difference in DMI among treatments was observed, and there was no interaction between treatments and vaccinations (Table 2). Average daily DMI of goats were 681.2, 700.6, and 716.9 g/d (before vaccination) and 682.7, 677.9, and 689.8 g/d (after vaccination) in the control, CADI, and GABA treatments, respectively.

On the other hand, there was difference among treatments in ADG by vaccination (\( P < 0.01 \)), and a treatment × vaccination interaction was also observed (\( P < 0.05 \)). Average daily gain during the before vaccination week were 35.4, 43.7, and 134.3 g/d for control, CADI, and GABA group, respectively. Average daily gain of goats during the after vaccination week, however, significantly decreased in the control and GABA groups to \(-62.0 \) and \(-54.8 \) g/d, respectively. No reduction in ADG was observed in the CADI treatment (43.7 and 50.7 g/d during the week before and after the FMD vaccination, respectively). It indicated that CADI treatment attenuated the adverse effect of vaccination on growth.

Table 2. The effects of foot-and-mouth disease vaccination on growth performance and nutrient digestibility in goats

<table>
<thead>
<tr>
<th>Item</th>
<th>Control Before</th>
<th>Control After</th>
<th>CADI Before</th>
<th>CADI After</th>
<th>GABA Before</th>
<th>GABA After</th>
<th>SEM</th>
<th>Treatment</th>
<th>Vaccination</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMI, g/d</td>
<td>681.2</td>
<td>682.7</td>
<td>700.6</td>
<td>677.9</td>
<td>716.9</td>
<td>689.8</td>
<td>48.13</td>
<td>0.81</td>
<td>0.56</td>
<td>0.90</td>
</tr>
<tr>
<td>ADG, g/d</td>
<td>35.4</td>
<td>-62.0</td>
<td>43.7</td>
<td>50.7</td>
<td>134.3</td>
<td>-54.8</td>
<td>36.39</td>
<td>0.21</td>
<td>&lt;0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Digestibility, g/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>677.9</td>
<td>691.4</td>
<td>663.6</td>
<td>673.8</td>
<td>664.4</td>
<td>675.1</td>
<td>11.17</td>
<td>0.23</td>
<td>0.17</td>
<td>0.98</td>
</tr>
<tr>
<td>OM</td>
<td>712.7</td>
<td>713.8</td>
<td>698.2</td>
<td>700.0</td>
<td>701.6</td>
<td>698.8</td>
<td>10.29</td>
<td>0.24</td>
<td>1.00</td>
<td>0.96</td>
</tr>
<tr>
<td>CP</td>
<td>672.2</td>
<td>690.8</td>
<td>663.9</td>
<td>680.0</td>
<td>674.1</td>
<td>690.4</td>
<td>11.85</td>
<td>0.53</td>
<td>0.04</td>
<td>0.99</td>
</tr>
<tr>
<td>EE</td>
<td>812.6</td>
<td>795.5</td>
<td>796.5</td>
<td>785.7</td>
<td>812.8</td>
<td>779.8</td>
<td>9.69</td>
<td>0.40</td>
<td>0.01</td>
<td>0.49</td>
</tr>
<tr>
<td>aNDF</td>
<td>611.9</td>
<td>629.3</td>
<td>589.2</td>
<td>607.2</td>
<td>590.8</td>
<td>609.1</td>
<td>14.58</td>
<td>0.23</td>
<td>0.13</td>
<td>1.00</td>
</tr>
<tr>
<td>ADF</td>
<td>606.2</td>
<td>634.0</td>
<td>599.0</td>
<td>599.6</td>
<td>559.5</td>
<td>630.7</td>
<td>18.69</td>
<td>0.44</td>
<td>0.05</td>
<td>0.26</td>
</tr>
</tbody>
</table>

1 CADI = co-injection of commercially available dipyrone.
2 GABA = gamma-aminobutyric acid.
3 Interaction between treatments and vaccination.
4 EE = ether extract.
5 aNDF = amylase-treated NDF; analyzed using heat stable amylase and expressed inclusive of residual ash.

Nutrients Digestibility and Nitrogen Utilization

Apparent digestibility of CP and ADF was increased by vaccination regardless of treatment (\( P < 0.05 \)), which did not differ significantly among the treatments (Table 2). Reduction in EE digestibility by vaccination was observed (\( P < 0.05 \)).

No interaction between treatment and vaccination was observed in the digestibility of nutrients.

No significant difference in intake, excretion, or retention of N was observed by treatment, vaccination, and interaction between treatment and vaccination (Table 3). Vaccination, however, decreased the ratio of fecal nitrogen excretion to ingested nitrogen (\( P < 0.05 \)), which implied that there was trend of reduction in fecal nitrogen excretion by vaccination.

Hematological Parameters

Leukocyte counts (i.e., total white blood cells, lymphocyte, monocyte, neutrophil, eosinophil, and basophil) increased after the vaccination (\( P < 0.01 \); Table 4). The neutrophil to lymphocyte ratio (N:L) after the vaccination (0.61) was also higher (\( P < 0.01 \)) than that before vaccination (0.31). No significant change was observed in leukocyte counts by treatment or interaction between treatment and vaccination. On the contrary, erythrocyte count, hematocrit (relative volume of erythrocytes), and hemoglobin concentration decreased after the vaccination (\( P < 0.05 \)). The value of hematocrit and the number of red blood cells tended to be different among treatments (\( P = 0.05 \) and \( P = 0.06 \), respectively). Especially after vaccination, the CADI treatment tended to have higher hematocrit (\( P = 0.09 \)). No significant interaction between treatment and vaccination was observed in the parameters for erythrocytes.
Behavioral Observation

The FMD vaccination increased the time spent in standing and decreased the time spent in lying of the goats ($P < 0.05$). Co-injection of commercially available dipyrone successfully attenuated these effects. After the vaccination, the time spent in standing and lying of the CADI treated goats were different ($P < 0.05$) from the control or GABA groups (Fig. 2). After the vaccination the time spent in drinking of the goats was also increased ($P < 0.05$), and there was a significant difference in the time spent in drinking between the control and CADI groups after vaccination. There was no difference in the time of goats spent eating in relation to vaccination or treatment.

DISCUSSION

From November 2010 to January 2011, a serious outbreak of FMD disease occurred in South Korea, and it is a regulatory requirement for a farmer to have documentation (i.e., a certificate) that his goats, cattle, and pigs are FMD vaccinated since then. Without a proof of FMD vaccination, a farmer is not allowed to sell his animals or animal products. The FMD vaccine has been shown to reduce local virus replication and virus circulation (Barnett and Carabin, 2002; Barnett et al., 2004). Although vaccination against disease is effective in preventing cattle and sheep from targeted viral infection (Orsel and Bouma,

Table 3. The effects of foot-and-mouth disease vaccination on nitrogen utilization in goats

<table>
<thead>
<tr>
<th>Item</th>
<th>Control</th>
<th>CADI</th>
<th>GABA</th>
<th>SEM</th>
<th>$P$-value</th>
<th>Treatment</th>
<th>Vaccination</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrient utilization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N intake, g/d</td>
<td>11.6</td>
<td>11.6</td>
<td>12.0</td>
<td>11.6</td>
<td>12.5</td>
<td>12.1</td>
<td>0.82</td>
<td>0.45</td>
</tr>
<tr>
<td>Fecal N, g/d</td>
<td>3.8</td>
<td>3.7</td>
<td>3.9</td>
<td>3.6</td>
<td>4.0</td>
<td>3.7</td>
<td>0.28</td>
<td>0.85</td>
</tr>
<tr>
<td>Urinary N, g/d</td>
<td>4.3</td>
<td>4.4</td>
<td>4.3</td>
<td>4.2</td>
<td>4.0</td>
<td>4.3</td>
<td>0.41</td>
<td>0.81</td>
</tr>
<tr>
<td>N excreted, g/d</td>
<td>8.0</td>
<td>8.0</td>
<td>8.2</td>
<td>7.9</td>
<td>8.0</td>
<td>8.0</td>
<td>0.63</td>
<td>0.99</td>
</tr>
<tr>
<td>Retained N, g/d</td>
<td>3.5</td>
<td>3.6</td>
<td>3.7</td>
<td>3.7</td>
<td>4.6</td>
<td>4.1</td>
<td>0.55</td>
<td>0.27</td>
</tr>
<tr>
<td>Biological value</td>
<td>0.41</td>
<td>0.41</td>
<td>0.45</td>
<td>0.45</td>
<td>0.50</td>
<td>0.46</td>
<td>0.050</td>
<td>0.29</td>
</tr>
<tr>
<td>Fecal N ratio</td>
<td>0.33</td>
<td>0.31</td>
<td>0.34</td>
<td>0.32</td>
<td>0.32</td>
<td>0.31</td>
<td>0.012</td>
<td>0.53</td>
</tr>
<tr>
<td>Urinary N ratio</td>
<td>0.39</td>
<td>0.40</td>
<td>0.36</td>
<td>0.37</td>
<td>0.33</td>
<td>0.36</td>
<td>0.033</td>
<td>0.28</td>
</tr>
</tbody>
</table>

1 CADI = co-injection of commercially available dipyrone.
2 GABA = gamma-aminobutyric acid.
3 Interaction between treatments and vaccination.
4 N intake – (fecal N + urinary N).
6 Fecal N/N intake.
7 Urinary N/N intake.

Table 4. The effects of foot-and-mouth disease vaccination on hematological response in goats

<table>
<thead>
<tr>
<th>Item</th>
<th>Control</th>
<th>CADI</th>
<th>GABA</th>
<th>SEM</th>
<th>$P$-value</th>
<th>Treatment</th>
<th>Vaccination</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC, $10^3/\mu$L</td>
<td>11.7</td>
<td>17.3</td>
<td>12.9</td>
<td>17.4</td>
<td>12.8</td>
<td>16.8</td>
<td>1.44</td>
<td>0.66</td>
</tr>
<tr>
<td>Lymphocytes, $10^3/\mu$L</td>
<td>5.6</td>
<td>6.9</td>
<td>6.3</td>
<td>6.6</td>
<td>6.7</td>
<td>6.9</td>
<td>0.70</td>
<td>0.15</td>
</tr>
<tr>
<td>Monocytes, $10^3/\mu$L</td>
<td>3.1</td>
<td>4.9</td>
<td>3.7</td>
<td>5.2</td>
<td>3.6</td>
<td>4.8</td>
<td>0.50</td>
<td>0.28</td>
</tr>
<tr>
<td>Neutrophils, $10^3/\mu$L</td>
<td>2.4</td>
<td>4.1</td>
<td>1.7</td>
<td>3.9</td>
<td>1.5</td>
<td>3.5</td>
<td>0.55</td>
<td>0.36</td>
</tr>
<tr>
<td>Eosinophils, $10^3/\mu$L</td>
<td>0.4</td>
<td>1.0</td>
<td>0.8</td>
<td>1.3</td>
<td>0.8</td>
<td>1.2</td>
<td>0.24</td>
<td>0.36</td>
</tr>
<tr>
<td>Basophils, $10^3/\mu$L</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.03</td>
<td>0.12</td>
</tr>
<tr>
<td>N:L</td>
<td>0.4</td>
<td>0.6</td>
<td>0.3</td>
<td>0.6</td>
<td>0.2</td>
<td>0.6</td>
<td>0.09</td>
<td>0.84</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC, $10^5/\mu$L</td>
<td>18.0</td>
<td>16.9</td>
<td>18.7</td>
<td>17.7</td>
<td>17.9</td>
<td>16.5</td>
<td>0.67</td>
<td>0.06</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>29.8</td>
<td>28.8</td>
<td>31.3</td>
<td>30.1</td>
<td>29.9</td>
<td>27.4</td>
<td>1.21</td>
<td>0.05</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.8</td>
<td>10.6</td>
<td>11.7</td>
<td>11.3</td>
<td>11.7</td>
<td>10.6</td>
<td>0.46</td>
<td>0.55</td>
</tr>
</tbody>
</table>

1 CADI = co-injection of commercially available dipyrone.
2 GABA = gamma-aminobutyric acid.
3 Interaction between treatments and vaccination.
4 WBC = white blood cell.
5 N:L = neutrophil to lymphocyte ratio.
6 RBC = red blood cell.
Effect of foot-and-mouth disease vaccination

(2009), it has been shown that vaccination may lead to adverse effects on animal productivity.

Several studies reported vaccinated animals had a reduction in growth and feed intake compared to the unvaccinated animals including aquatic and domestic species. Studies found that vaccinated salmon resulted in reduced feed intake and growth rate (Sørum and Damsgård, 2004; Berg et al., 2006). Vaccinated chicks showed lower BW gain and feed intake than nonvaccinated chicks (El-Sayed et al., 2011). In horse, a side effect of local swelling at the site of injection was reported, which led to a decrease in appetite or weight loss (Perkins et al., 2011). In ruminant animals, a previous study of growing beef heifers reported that growth of heifers was significantly reduced by the *Mannheimia haemolytica* vaccine (Arthington et al., 2013), although DMI was not depressed. Milk production was significantly reduced by vaccination against bovine herpesvirus 1 (*BHV*-1), bovine viral diarrhea virus (*BVDV*), parainfluenza-3 virus (*PI*-3V), and bovine respiratory syncytial virus (*BRSV*; Bosch et al., 1997; Scott et al., 2001; Bergeron and Elsener, 2008).

Only a few studies have been conducted to assess the side effects owing from the FMD vaccination. A previous study reported averagely 21.5% loss in milk production of lactating dairy cows for 7 consecutive days after the FMD vaccination (Yeruham et al., 2001). Adverse effects of the FMD vaccine on reproductive performance have also been demonstrated in Europe (Nusinovici et al., 2011). However, there is limited knowledge about the effects of FMD vaccines on the growth performance in ruminants, and to the best of our knowledge this study is the first scientific report that showed the adverse effect of the FMD vaccination in behavioral, physiology, and growth performance of the ruminant.

In this study, we showed that the FMD vaccination reduced growth performance in ruminant animals, which was not due to a decrease in intake or nutrients digestibility. There was no significant effect of the FMD vaccination on DMI, while the vaccination significantly decreased growth rate of the goats. Interestingly enough, digestibility of nutrients tended to increase after the FMD vaccination except for digestibility of EE. Digestibility of CP and ADF were significantly increased, and that of EE was significantly decreased. These results were consistent with a previous study with heat stressed lactating cows. McDowell et al. (1969) reported that by heat stress digestibility of CP and ADF slightly increased while that of EE was significantly reduced in lactating dairy cows. They speculated that the rate of passage through the digestive tract might be depressed and digestion of nutrients was enhanced consequently. Other studies were also investigated that the negative relationship between the passage rate and DM

![Figure 2](image-url). Behavioral changes by vaccination against foot-and-mouth disease. (a) Time spent in standing with control (♦), co-injection of commercially available dipyrone (CADI; ■), and γ-aminobutyric acid (GABA; ▲). (b) Time spent in lying with control (♦), CADI (■), and GABA (▲). (c) Time spent in eating with control (♦), CADI (■), and GABA (▲). (d) Time spent in drinking with control (♦), CADI (■), and GABA (▲). a–cMeans that do not have common superscripts differ \( P < 0.05 \).
digestibility was observed under hot environment on steers and heifers (Miaron and Christopherson, 1992; Bernabucci et al., 1999). It therefore seems to be reasonable to hypothesize that the flow of digesta in the gastrointestinal tract is reduced in vaccinated animals. Nonetheless, further research is needed to test this hypothesis. It is uncertain why digestibility of EE was depressed by the FMD vaccination, although it seems to be clear that metabolism of nutrient such as lipid and protein could be altered due to keep a homeorhetic state in animals that challenge their immune system as reported previously (Spurlock, 1997). In addition, Wellen and Hotamisligil (2005) also said that metabolism and immunity are closely linked.

Based on the changes in hematological parameters after the FMD vaccination in this study, the FMD vaccination seemed to induce inflammatory response to all goats and no significant difference in the parameters among treatments. It is widely accepted that the neutrophil counts and N:L reflect systemic inflammation and stress of an animal (Zahorec, 2001; Davis et al., 2008). In our study, the total number of leukocytes was increased ($P < 0.01$) with a predominant elevation of the myeloblast-origin leukocytes (i.e., monocyte, neutrophil, eosinophil, and basophil) after the FMD vaccination. The number of neutrophils and N:L in this study was doubled after the vaccination regardless of treatment. Although both inflammation and stress increase the neutrophil counts and N:L, a concurrent decrease in the number of lymphocytes is generally observed in the response to stress (Davis et al., 2008; O’Loughlin et al., 2011), which was not the case in our study.

Animals react to vaccination by an alteration of behavioral and physiological responses (Deiss et al., 2009), and it may affect production performance of animals (Caroprese et al., 2010). Goats spent more time in lying and drinking and less time in standing after vaccination. The results obtained in the present study agreed with previous studies in sick and stressed animals. Pig castrated spent more time lying and less time standing than noncastrated pig (McGlone et al., 1993; Sutherland et al., 2012). Hay et al. (2003) also showed that castrated piglets altered their behavior towards extended time spent lying (i.e., lying, sitting, and kneeling) and shortened time spent standing than noncastrated piglet for 5 d. In addition, sick calves had a greater frequency and duration of drinking than normal calves after 4 to 5 d (Buhman et al., 2000). In contrast, Ting et al. (2003a) reported more standing and less lying posture in castrated bulls compared with noncastrated bulls during the first 6 h after treatment. However, the length of observation in their study was short, and the animals might not be comfortable with lying posture right after castration.

Practical strategies might be necessary to attenuate the side effects of vaccination, and several approaches have been studied to reduce these side effects in animals in terms of stress. The application of oral electrolyte therapy has been reported to reduce physical stress of cattle during transport and handling (Schaef et al., 1997). There are some reports that feeding supplements with antioxidant activity (i.e., vitamins and polyphenols) improved stress tolerance in ruminant animals (Fike et al., 2001; Saker et al., 2004; Sgorlon et al., 2006). In particular, effect of analgesic drug administration on plasma cortisol response in castrated calves was reported in various studies (see a review by Coetzee, 2011). Ting et al. (2003a) proposed that ketoprofen would be beneficial for alleviation of acute stress response (i.e., cortisol) in surgical castration of bulls. A similar result was observed that carprofen administration before castration bulls reduced the integrated cortisol response and acute phase protein production without altering DMI or ADG (Pang et al., 2006).

In this study we evaluated 2 possible practices for reducing the adverse effects by the FMD vaccination. One practice tested was to supplement 10 g/kg GABA in concentrate mix. Gabapentin, a GABA analogue, is used in management of chronic pain in human (Petroff et al., 1996). Subsequent studies have established that gabapentin is effective for the management of chronic pain of inflammatory or neuropathic origin (Fraccaro et al., 2013). When oral gabapentin capsule (10 mg/kg BW) or gabapentin powder (15 mg/kg BW) with NSAID were administered to beef calves, chronic pain was significantly reduced in cattle (Coetzee et al., 2011). In addition, the GABA supplementation (100 mg/kg BW) significantly increased weight gain and feed consumption and slightly increased BW in heat-stressed broiler chicks (Dai et al., 2011). Growth performance of stressed chicks was also enhanced by the supplementation of GABA at 40 to 80 mg/kg BW (Xie et al., 2013). The effectiveness of oral administration of gabapentin (20 mg/kg) was lower than intravenous gabapentin (30 to 90 mg/kg) in nerve-injured rat (Terry et al., 2010). However, little is known on the effect of dietary GABA on stress attenuation in vaccinated ruminants.

The GABA treatment group in this study showed numerically higher ADG (134.3 g/d) on the week before the FDM vaccination compared to control and CADI treatment groups (35.4 and 43.7 g/d). However, supplementation of GABA had no effect on ADG of goats after vaccination, and adverse effects by the FMD vaccination was not reduced by GABA. No difference between the control and GABA groups was found in growth performance, nutrients digestibility, nitrogen utilization, behavior, or hematological parameters. No effect of supplementation of GABA for attenuation of adverse effects of vaccination was observed in this study.

The amount of active GABA supplied to the animals was 1.4 g/kg of dietary DM. Although the level of supplementation of GABA was much higher than that in the study showed an increase DMI and improved milk protein yield in transition cows by supplementing rumen-protected
GABA at the level of 1.2 g/d, equivalent to 0.12 g/kg of dietary DM (Wang et al., 2013), the level had been chosen to supply sufficient amount of GABA to the animals considering ruminal degradation. Nonetheless, there is still a possibility that the dosage of GABA in this study may not be enough to be effective. The dose of ruminally nonprotected GABA used in Van Os et al. (1996) and Dawson and Mayne (1997) were 5 and 6 g/kg DM, respectively.

On the other hand, co-injection of the FMD vaccination with CADI successfully attenuated the adverse effect of FMD vaccination on growth rate and behavior of goats. No difference in hematological parameters between the control and CADI groups indicated that the goats in the CADI group were also stressed by the FMD vaccination. However, the vaccination stress led to neither behavioral change (i.e., standing and lying time) nor growth depression in CADI treatment group. Nonsteroidal anti-inflammatory drugs, including dipyrone, ibuprofen, ketoprofen, and meloxicam, can be useful systemic analgesics depending on the severity of the pain (Dionne and Berthold, 2001; Rault et al., 2011). The analgesia produced by these NSAID is related to the potent inhibitory effect on prostaglandin production, and NSAID is reported to have anti-inflammatory and antipyretic properties (Selinsky et al., 2001). Nonsteroidal anti-inflammatory drugs produce analgesia primary through their anti-inflammatory actions, but they also have direct central analgesic actions, which vary according to drugs (McMeekan et al., 1998). Nonsteroidal anti-inflammatory drugs prevent inflammation by inhibiting cyclooxygenase, the enzyme involved in the synthesis of prostanoids, which contribute to pain (Fraccaro et al., 2004). Co-injection of commercially available dipyrone, therefore, seems to reduce inflammatory response of the goats affected by the FMD vaccination and attenuate the side effects of vaccination response in growth and behavior. However, it needs to be pointed out that dipyrone is not approved for marketing in the United States and many European countries, although it is commonly used by humans in some countries. A kind of NSAID, ketoprofen, was effective in decreasing the inflammatory and the stress response associated with castration (Dawson, L. E. R., and C. S. Mayne. 1997). The effect of infusion of putrescine and gamma amino butyric acid on the intake of steers offered grass silage containing three levels of lactic acid. Anim. Feed Sci. Technol. 66:15–29.

In conclusion, the FMD vaccination decreased ADG of the animals without depression of feed intake. Co-injection of commercially available dipyrone attenuated the adverse effect of the FMD vaccination on growth possibly by reducing the side effects of inflammatory response following the FMD vaccination.


