

## Evaluation of Isotonic Sodium Bicarbonate Solution for Alkalinizing Effects in Conscious Calves

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**ABSTRACT.** After intravenous (IV) infusion of various volumes of 1.35%-isotonic sodium bicarbonate solution (ISB), acid-base equilibrium, blood pressure, plasma volume and biochemical parameters in healthy Holstein calves were studied. Four calves each were randomly assigned to the low-dose (LD; IV infusion of 5 ml/kg ISB), middle-dose (MD; IV infusion of 10 ml/kg ISB) and the high-dose groups (HD; IV infusion of 15 ml/kg ISB). Administration volumes of ISB in the LD, MD and HD groups were decided based on the first half volumes of 5, 10 and 15 mEq of base requirement by the acceptable equation. Systemic, pulmonary artery and central venous pressures, cardiac output and plasma osmotic pressure were not changed by ISB infusion and remained constant throughout the experiment for all groups. There was good correlation ( $r^2 = 0.950$ ) between relative changes in base excess and infused volume of bicarbonate ( $y=2.491x$ ). The coefficient of distribution for bicarbonate ions was calculated to be 0.401 ( $=1/2.491$ ). Therefore, it is suggested that a value of 0.4 would be most appropriate when calculating the base requirements in calves. Therefore, the first half volumes of ISB correcting base deficits of 5, 10 and 15 mEq in calves were estimated to be 6, 12 and 18 ml/kg, respectively. On the basis of the findings in this study, ISB may be used to correct metabolic acidosis without altering the plasma osmotic pressure, hemodynamic status and respiratory function in the calves.

**KEY WORDS:** acid-base equilibrium, calf, coefficient of distribution, metabolic acidosis, sodium bicarbonate.

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When calves severely affected by diarrhea become dehydrated and develop metabolic acidosis, one objective of treatment is to correct these problems [13, 14, 23]. Administration of oral rehydrated fluids to a dehydrated calf is performed on a daily basis in veterinary practice [2, 16]. If treatment with oral fluids is not successful, intravenous restoration of an acid-base disorder is preferred. The sodium salts of acetate, lactate, gluconate and bicarbonate are available for parenteral use as alkalinizing agents in proprietary extracellular replacement fluids [8, 10, 13, 17]. Although lactated Ringer's solution is used to replace the volume of total body water and electrolyte deficits, it will not usually correct the metabolic acidosis in calves with diarrhea [22, 25]. Sodium bicarbonate is specifically effective for acute, severe metabolic acidosis, because it has rapid effect when given intravenously (IV) [7–11, 17]. Sodium bicarbonate solution, the alkalinizing agent of choice, is most often used as a 7.0% hypertonic solution that is commercially available in Japan. Nevertheless, rapid administration of, or an overdose with hypertonic sodium bicarbonate solution has been associated with extracellular fluid hyperosmolarity, paradoxical cerebrospinal fluid acidosis, leftward shift of the oxyhemoglobin dissociation curve leading to decreased downloading of oxygen, intracellular shift of K in exchange for hydrogen ions causing hypokalemia, transient hypernatremia possibly inducing volume overload, tetany due to decreased ionized calcium, and overshoot alkalosis [1, 7]. Abrupt changes in osmolarity can lead to cerebral hemorrhage due to alternations in electrolytes, water and acid-base status [3, 7]. If an

isotonic sodium bicarbonate (1.35% NaHCO<sub>3</sub>) solution (ISB) can restore the rehydration and acid-base equilibrium without hyperosmolarity, it can be used to treat dehydrated calves with metabolic acidosis. Therefore, the alkalinizing effects and apparent volume correcting metabolic acidosis in calves must be confirmed before ISB can be recommended as the initial method for treatment of calves with severe diarrhea and metabolic acidosis.

The primary purpose of this study was to evaluate the relationship between correcting the base deficit and the apparent volume of ISB in calves with ISB in parenteral fluid therapy. Additional objectives included comparing the hemodynamic status, blood gases and serum electrolytes with a first half volume of 5, 10 and 15 mEq/l of the base requirement given to calves for clinical usefulness.

### MATERIALS AND METHODS

Experiments were performed on 12 healthy  $28.2 \pm 3.5$ -day old Holstein breed male calves weighing  $57.5 \pm 6.8$  kg. The calves were deemed healthy on the basis of physical examination, electrocardiography, and hematological analysis. The calves were fed a completely balanced growth diet consisting of a pelleted concentrated ration and mixed grass hay and had unlimited access to fresh water.

The day before an experiment, all calves were sedated with an IV infusion of xylazine hydrochloride (Seduluck-2%; Nippon Zenyaku Kogyo, Co., Ltd, Fukushima, Japan) at a dosage of 0.2 mg/kg of body weight. An 8-F introducer

(Fast-Cath™; NihonKohden, Tokyo, Japan) was placed in the left jugular vein. A 14-gauge, 40-cm length arterial and a 14-gauge, 35-cm length venous catheter (Sefelet Catheter NCKP-14-70; Nipro Co., Osaka, Japan) were inserted in the right femoral artery and vein, respectively. Both catheters were used for collection of arterial and venous blood samples. At least 24 hr elapsed after femoral catheterizations until ISB was infused. Approximately 1 hr before ISB infusion, a 16-gauge catheter (Sefelet Catheter NSL-16WOT, Nipro) was implanted percutaneously into the right jugular vein for infusion of the ISB. A balloon-tipped, flow-directed thermodilution catheter (Thermodilution Catheter TC-704; Nihon Kodan), which was used for measurement of cardiac output (CO), central venous pressure (CVP) and pulmonary arterial pressure (PAP), was inserted into the left jugular vein via the introducer. This catheter was positioned with the proximal port in the right atrium and the distal port and thermistor in the pulmonary artery. Various pressures (systemic, CVP and PAP) were measured with a galvanometric recorder (BP-308ETI; Nihon Kodan) with a strain-gauge transducer (Model DX-360; Nihon Kodan) positioned at the level of the point of the shoulder [24]. All catheter positions were confirmed by evidence of characteristic pressure wave forms [24]. A continuous base-apex electrocardiograph and blood temperature were also monitored. Food and water were withheld from calves during the experiment.

All calves received an IV infusion of the ISB via an infusion pump (PRS-25; Nikkiso Co., Tokyo). Calves were randomly assigned to the low-dose (LD: IV infusion of 5 ml/kg-ISB), the middle-dose (MD: IV infusion of 10 ml/kg-ISB) and the high-dose (HD: IV infusion of 15 ml/kg-ISB) groups of 4 calves each. Calves in the all groups received an IV infusion of the various volumes of ISB, over the 30 min. Administration volumes of ISB in the LD, MD and HD groups were decided based on the first half volumes of 5, 10 and 15 mEq of the base requirement. The infused volume of bicarbonate was derived from: Base needed (mEq)=BW (kg) × Base Requirement (mEq/l) × 1/3 (l/kg) [12].

The initiation of infusion of ISB was designated as time 0. All calves were then monitored for 180 min. Arterial and venous samples were collected at time 0 (pre), and 5, 10, 15, 30, 45, 60, 90, 120, 150 and 180 min after the initiation of infusion of ISB. Immediately before the collection of each blood sample, systolic, diastolic, and mean systemic pressures (SAP, DAP, MAP), and mean CVP and PAP, heart rate (HR) and abnormal signs were recorded. Arterial and venous blood samples were collected anaerobically in a heparinized 1-ml syringe, and then the tips of the syringes were immediately capped. Immediately after collection was completed, CO was determined with a thermodilution computer after ice isotonic NaCl (5 ml) was injected into the right atrium at end-expiration of the ventilatory cycles. All CO measurements were performed in triplicate, and the mean value was determined for the 3 values. The cardiac index (CI: CO/body surface area [BSA], l/min/m<sup>2</sup>), stroke volume (SV: CO/HR, l/beat), systemic vascular resistance

(SVR: MAP/CO, mmHg/l/min) and pulmonary vascular resistance (PVR; mean PAP/CO, mmHg/l/min) were calculated [6]. The BSA was derived from the following equation: BSA (m<sup>2</sup>)=(BW<sup>2/3</sup> × 10.1)/100 [18, 19].

Blood samples were analyzed for pH and blood gases with an automatic gas analyzer at 37°C (model 248; Bayer Medical, Tokyo). All samples were analyzed within 5 min of collection. The measured values were automatically corrected to correspond to each calf's blood temperature. Some venous blood samples were used to determine the hemoglobin concentration (Hb) and hematocrit value (Ht) with an automatic cell counter (MEK-6248; Nihon Kodan). Changes in the relative plasma volume (rPV) were calculated from Hb and Ht, with accepted formulas [5, 21]. Relative changes in base excess (rBE) were derived from the following equation: rBE = BE<sub>samp</sub> - BE<sub>pre</sub>, where BE<sub>samp</sub> and BE<sub>pre</sub> were BE concentrations in each sampling and pre point, respectively. Other venous blood samples were centrifuged, and plasma was collected and stored at -20°C. The concentrations of ionized sodium (Na), potassium (K) and chloride (Cl) in the plasma were analyzed by the electrode methods, with an automatic analyzer (model 644; Nihon Kodan). Plasma osmotic pressure was determined by the freezing point depression method, with an automatic osmometer (One-Ten Osmometer; Fiske Co., Norwood, MA, U.S.A.).

Data are shown as the means ± SD. Data were analyzed by means of repeated-measures analysis of variance (ANOVA). The variables included in the model were time, ISB infusion, and interaction of time and fluid infusion. The BE at the end of the ISB infusion and infused volume of sodium bicarbonate were evaluated by liner regression analysis. The significance level was *p*<0.05.

## RESULTS

All calves were clinically normal before the experiment, as determined on the basis of vital signs, attrition, food and water intake, and urine and feces production. Clinical signs, such as moist rales on auscultation, moist cough, jugular vein congestion, ophthalmoptosis, salivation or arrhythmia, were not observed throughout the experiment. The pre values of HR, SAP, DAP, MAP, CVP and PAP were 78.3 ± 14.1 bpm, 133.6 ± 11.0, 74.1 ± 8.7, 100.2 ± 9.4, 5.7 ± 3.8 and 21.5 ± 4.9 mmHg, respectively. Hemodynamic variables that were measured (HR, SAP, DAP, MAP, CVP and PAP) were not changed by ISB infusion and remained constant throughout the experiment in all groups. The pre values of CO, CI, SV, SVR and PVR were 11.5 ± 2.1 l/min, 5.2 ± 0.5 l/min/m<sup>2</sup>, 0.138 ± 0.028 l/beat, 8.9 ± 1.6 mmHg//min and 1.9 ± 0.4 mmHg/l/min, respectively. Those calculated parameters of hemodynamic status were also not changed by ISB infusion and remained constant throughout the experiment in the all groups. Sequential changes in rPV were monitored in calves which received ISB infusion. The rPV of the LD group increased slightly, and then jumped to the pre values at 120 min after the initiation of ISB infusion. The rPV in

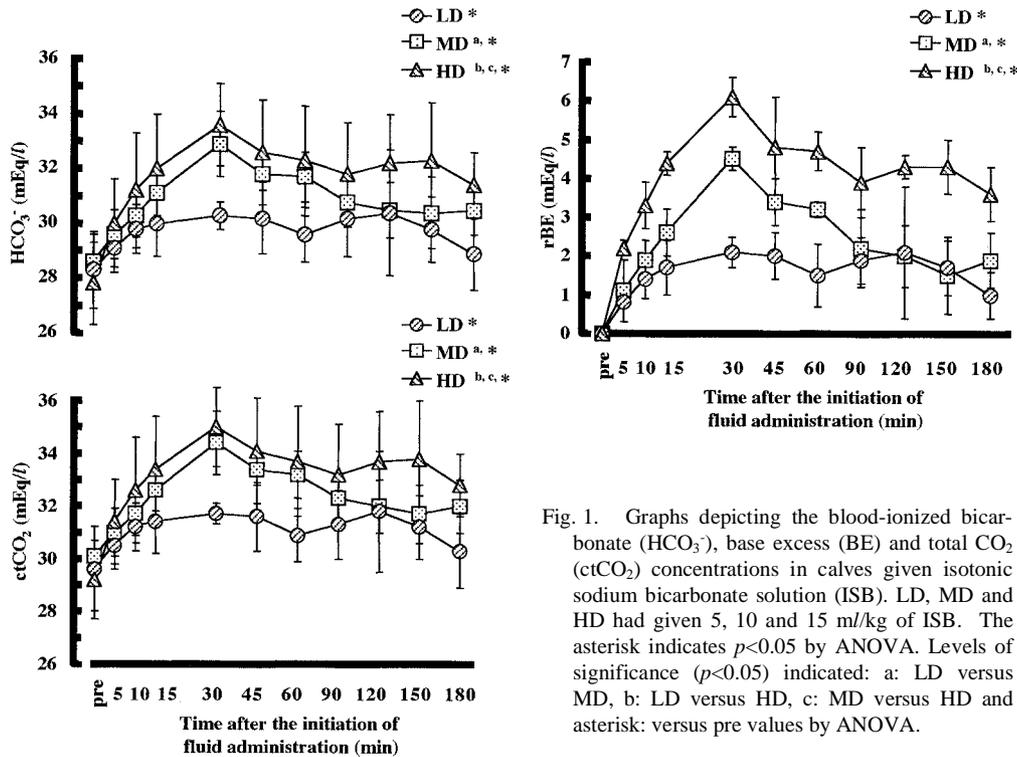


Fig. 1. Graphs depicting the blood-ionized bicarbonate ( $\text{HCO}_3^-$ ), base excess (BE) and total  $\text{CO}_2$  ( $\text{ctCO}_2$ ) concentrations in calves given isotonic sodium bicarbonate solution (ISB). LD, MD and HD had given 5, 10 and 15 ml/kg of ISB. The asterisk indicates  $p < 0.05$  by ANOVA. Levels of significance ( $p < 0.05$ ) indicated: a: LD versus MD, b: LD versus HD, c: MD versus HD and asterisk: versus pre values by ANOVA.

the MD and HD groups increased significantly until the end of the ISB infusion, and were significantly greater than that in the LD groups ( $p < 0.05$ ). The values at the end of fluid infusion (t=30) of rPV in the LD, MD and HD groups were  $106.9 \pm 3.6$ ,  $111.9 \pm 1.9$  and  $113.0 \pm 6.2\%$ , respectively. No significant difference was observed between the MD and HD groups in the sequential changes in rPV.

Figure 1 shows the venous ionized bicarbonate ( $\text{HCO}_3^-$ ), base excess (BE) and total carbon dioxide ( $\text{ctCO}_2$ ) concentrations in calves given ISB infusion. The pre values of  $\text{HCO}_3^-$  concentrations in the LD, MD and HD groups were  $28.3 \pm 1.4$ ,  $28.6 \pm 1.0$  and  $27.8 \pm 1.5$  mEq/l, respectively. A 5, 10 or 15 ml/kg-ISB infusion induced significant increases in the  $\text{HCO}_3^-$  level, reaching  $30.3 \pm 0.5$ ,  $32.9 \pm 1.2$  and  $33.6 \pm 1.5$  mEq/l at the end of ISB infusion (t=30 min), respectively ( $p < 0.05$ ). The  $\text{HCO}_3^-$  level of the LD group then returned to the pre values at end of experiment. In contrast, the increasing  $\text{HCO}_3^-$  level of the MD and HD groups remained up to 1.8 and 3.6 mEq/l higher than the pre values until the end of the entire 180 min, respectively. Changes of  $\text{ctCO}_2$  followed the pattern similar to that of  $\text{HCO}_3^-$ . The pre values for  $\text{ctCO}_2$  in the LD, MD and HD groups were  $29.6 \pm 1.6$ ,  $30.1 \pm 1.1$  and  $29.2 \pm 1.5$  mEq/l, respectively. Infusing of 5, 10 and 15 ml/kg of ISB significantly induced an increase in  $\text{ctCO}_2$ , making it to  $31.7 \pm 0.4$ ,  $34.4 \pm 1.2$  and  $35.0 \pm 1.5$  mEq/l at the end of the ISB infusion, respectively ( $p < 0.05$ ). Sequential changes in BE were monitored in calves receiving ISB infusion. The pre values of BE in LD, MD and HD groups were  $3.1 \pm 1.0$ ,  $2.9 \pm 1.0$  and  $2.7 \pm 1.7$  mEq/l, respectively. The BE in LD, MD and HD groups

were significantly increased from the pre values until the end of ISB infusion, reaching  $5.2 \pm 0.7$ ,  $7.4 \pm 1.0$  and  $8.8 \pm 1.7$  mEq/l, respectively ( $p < 0.05$ ). The rBE at the end of ISB infusion in LD, MD and HD groups were  $2.1 \pm 0.4$ ,  $4.5 \pm 0.3$  and  $6.1 \pm 0.5$  mEq/l, respectively. There was good correlation between rBE and total amount of base infused ( $y = 2.491x$ ), with correlation coefficient of 0.950 ( $p < 0.001$ , Fig. 2). The coefficient of distribution for bicarbonate ions could be calculated to be 0.401 ( $= 1/2.491$ ). In all the groups, partial pressure of carbon dioxide ( $\text{PaCO}_2$ ), partial pressure of oxygen ( $\text{PaO}_2$ ), percentage oxygen saturation ( $\text{O}_2\text{sat}$ ) from the arterial blood samples remained at the pre values after the infusion of various dose of ISB. These variables were not significantly different among 3 groups.

Plasma Na concentration and osmotic pressure in all the groups were not changed by ISB infusion, and remained constant throughout the experiment. Figure 3 shows the plasma K and Cl concentrations in calves given ISB infusion. In the LD group, plasma K and Cl concentrations also remained constant throughout the experiment. However, plasma K and Cl concentrations in the MD and HD groups were progressively and significantly decreased until the end of ISB infusion, then increased sharply to the pre values ( $p < 0.05$ ). Sequential changes in plasma K and Cl concentrations in the HD group were significantly greater than those in the other groups ( $p < 0.05$ ).

## DISCUSSION

Intravenous infusion of a isotonic sodium bicarbonate

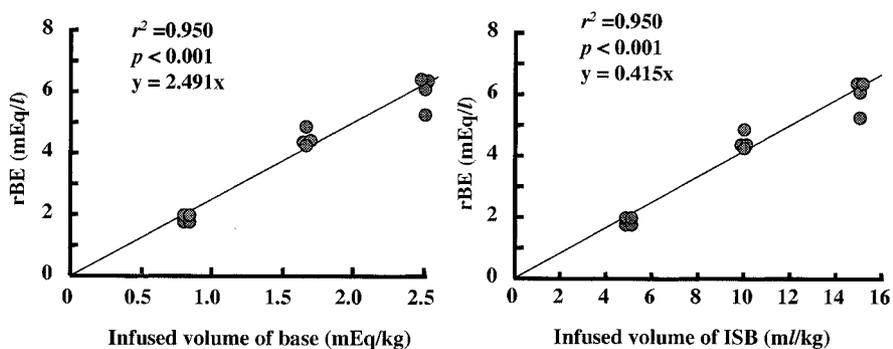


Fig. 2. Relationship between relative changes of base excess (rBE) and infused volume of bicarbonate in 12 calves. Solid line represents the liner regression line ( $r^2 = 0.950$ ,  $p < 0.001$ ).

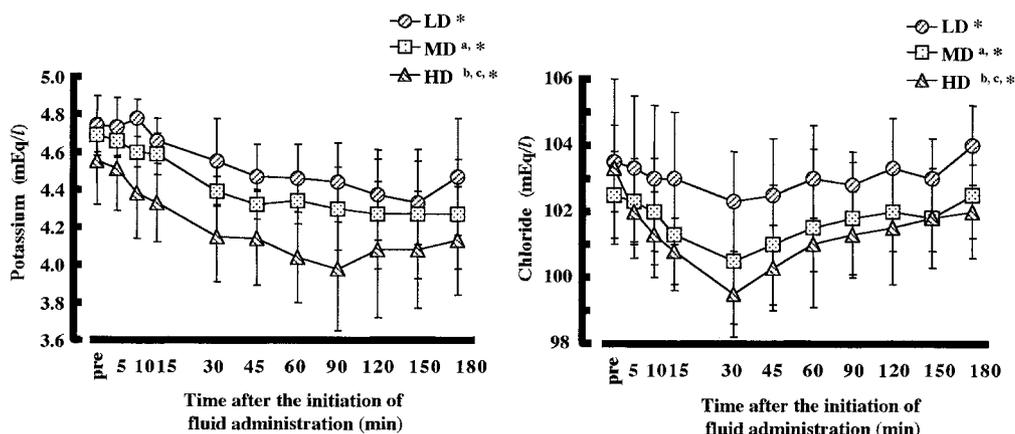


Fig. 3. Graphs depicting plasma potassium (K) and chloride (Cl) concentrations in calves given ISB. See Figure 1 for key.

solution in clinically normal, conscious,  $28.2 \pm 3.5$ -day old Holstein breed male calves was found to be safe and effective in increasing extracellular  $\text{HCO}_3^-$  concentration without altering the plasma osmotic pressure, hemodynamic status and respiratory function. In this study, there was good correlation between rBE and infused volume of bicarbonate ( $y=2.491x$ ), with correlation coefficient of 0.950. The coefficient of distribution for bicarbonate ions could be calculated to be 0.401. Therefore, IV infusion of ISB should be explored as a treatment for calves with metabolic acidosis. On the basis of the finding in this study, base deficits of 5, 10 and 15 mEq in calf could be calculated as fluid volumes of 6, 12 and 18 ml/kg of ISB, respectively.

Some diarrheic calves had a metabolic acidosis as evidenced by low blood pH, low bicarbonate concentrations and negative base excess values [1, 2, 8, 9, 13–15]. In treating a metabolic acidosis, the veterinarian must determine the dose and rate of administration of sodium bicarbonate. It is recommended that the first half of the deficits can be corrected over a period of about 30 min [7]. Therefore, we decided for the volumes of ISB based on the first half volume of 5, 10 and 15 mEq of base requirement. A large num-

ber of studies have used different recipes, calculation formulas, and rates of administration for correcting acidosis in calves [1]. In this study, base required was calculated using the following equation: base required (mEq) = base deficit (mEq/l)  $\times$  BW  $\times$  1/3 (l/kg) [12]. Therefore, infusion volume and flow rate of ISB in the LD, MD and HD groups could be calculated to be 5, 10 and 15 ml/kg, and 10, 20 and 30 ml/kg/hr, respectively.

Telltale signs were that the infusion rate, volume given or overshoot alkalosis was excessive. These included the development of moist rales on auscultation and the presence of moist cough or a serous nasal discharge [12]. When these signs appear, the fluid infusion should be slowed or be stopped. Venous congestion especially of the jugular vein and sustained rise of 4.4 mmHg in CVP should be also taken as signs that the infusion should be slowed or stopped [2, 4, 12]. In this study, the IV infusion of 5, 10, 15 ml/kg of ISB, over the 30 min, did not induce any abnormal clinical signs, and the increases in CVPs were less than 0.3, 0.5 and 1.3 mmHg during the infusion, respectively. In addition, ISB infusion did not alter the levels of  $\text{PaCO}_2$  and  $\text{PaO}_2$ , and the effect of ISB infusion on cardiovascular system was mini-

mal. Plasma Na concentration and osmotic pressure in all the groups were also not changed by ISB infusion. The plasma K concentration significantly decreased in the calves given ISB infusion. K moving from the extra- to intracellular compartment mediated by hydrogen ion may have caused this phenomenon. Although the Cl concentration in the plasma was decreased by the ISB infusions, the changes were not at the level to be of risk to the calves. On the basis of these findings, it is suggested that ISB can be safely infused into the calf.

The base needed from blood gasses analysis multiply base deficit with BW and with the coefficient of distribution for bicarbonate ions in the body. The coefficient of distribution represents the volume of bicarbonate in extracellular space. However, clinicians in the veterinary practice use various coefficients of bicarbonate distribution when calculating bicarbonate requirements (for example, 0.3 [20], 1/3 [12], 0.5 [2,11], or 0.6 [8, 26]). In this study, it is indicated that the apparent coefficient of distribution of bicarbonate was 0.401. Kasari and Naylor [11] demonstrated that the volume of distribution of bicarbonate in calves, whose mean weight was 47.5 kg, was 0.44. Therefore, it is suggested that 0.4 would be most appropriate when calculating base requirements in calves. In summary, the base requirements can be calculated using formula:

Bicarbonate required (mEq) = base deficit (mEq/l)  $\times$  BW  $\times$  0.4 (l/kg).

Therefore, the first half volumes of ISB correcting 5, 10 and 15 mEq of base deficit in calves were estimated to be 6, 12 and 18 ml/kg, respectively. On the basis of the findings in this study, ISB may be used to correct metabolic acidosis without altering the plasma osmotic pressure, hemodynamic status and respiratory function in the calves. Therefore, IV infusion of ISB should be explored as a treatment of dehydration and severe metabolic acidosis in calves with naturally occurring diarrhea.

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