

Effect of Isotonic and Hypotonic Lactated Ringer's Solutions with Dextrose Intravenously Administered to Dehydrated Heifers

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ABSTRACT. To determine the effects of rapid infusion of essential fluids in a volume of hypotonic lactated Ringer's solution, the central venous pressure (CVP) and acid-base equilibrium were investigated in to mildly dehydrated heifers. Mild dehydration was induced in 9 Holstein heifers by withholding food and water until $7.0 \pm 5.7\%$ of plasma volume had been lost. The heifers were randomly assigned to the ILG (lactated Ringer's + 5% dextrose), HLG (1/2 lactated Ringer's + 2.2% dextrose) or HRG (1/2 Ringer's + 2.5% dextrose) groups with 3 heifers in each group. Heifers received 30 ml/kg of one of the fluids, at a flow rate of 20 ml/kg/hr. The rapid intravenous (IV) infusions of HLG and HRG used in this study were found to be safe and effective in increasing plasma volume without increasing CVP, even though the infusion was given to the jugular vein at a dosage of 30 ml/kg. However, ILG infusion induced progressive increases in CVP, reaching 9.0 ± 2.0 mmHg. No clinical signs, such as moist rales on auscultation, moist cough, jugular vein congestion, ophthalmoptosis, salivation or arrhythmia, were observed throughout the fluid infusion. The relative changes in base excess (rBE) for the ILG and HRG groups were significantly decreased until the end of fluid infusion. As for the HLG group, rBE slightly decreased until the end of the fluid infusion. Then the values significantly increased and exceeded the pre-infusion value at the end of the experiment. While IV infusion of HLG inhibited acidification caused by dilution, HRG infusion induced diluted acidification. It is suggested that HLG infusion should be examined as a treatment for cattle with dehydration and moderate metabolic acidosis, since rapid infusion of HLG may be more beneficial for rehydrating cattle with metabolic acidosis than current treatment.

KEY WORDS: acid-base equilibrium, dehydration, heifer, hypotonic solution, plasma volume.

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Many diseases of cattle are characterized by severe acid-base and serum electrolyte disturbances, as well as dehydration. When the disturbances are severe or when the primary disease responsible for these imbalances cannot be readily corrected, parenteral or oral fluid and electrolyte replacement therapy must be initiated. Fluid and electrolyte replacement are indispensable therapies in modern cattle practice [4, 16], and rapid intravenous (IV) volume loading constitutes an important therapeutic measure for many critical cattle [4]. In the small number of laboratory data, a definite pattern of electrolyte and acid-base abnormalities are anticipated with some degree of confidence in mature cows suffering from a specific condition [1].

Lactated Ringer's solution, such as Hartmann's solution, is by far the most versatile of the fluids generally used in small animal practice [4-6]. This solution provides most electrolytes in a concentration similar to that of plasma. Persson *et al.* [15] suggested that hypotonic saline solution with 2.5% dextrose appeared to be the most appropriate solution when moderate dehydration of children had to be corrected in a short time. Another study showed that hypotonic Ringer's solution with 2.5% dextrose (HRG) did not change the plasma osmotic pressure or serum electrolyte balance in cattle and induced a proper reabsorption rate of glucose in the renal system [17, 18]. These results suggest that hypotonic solution is a better choice for rehydration therapy of mildly dehydrated cattle [17, 18].

Rehydration solutions can be grouped into alkalizing and non-alkalizing solutions. Alkalizing solutions contain bicarbonate or metabolic base that result in the consumption of a hydrogen ion when metabolized. Lactate is present as a bicarbonate precursor in lactated Ringer's solution at a concentration of 28 mEq/l [8]. If a hypotonic solution containing 28 mEq/l of sodium lactate can restore the rehydration and acid-base equilibrium of cattle, it could be used to treat cattle with moderate dehydration. Although alkalizing solutions are the foundation of rehydration therapy for small animal [5, 6], they are less frequently indicated for mature cattle. Therefore, to perform a safe and effective treatment, the choice of an appropriate fluid for the specific objectives and an understanding of the characteristics of physiological disturbances are critical.

The objectives of this study were to determine the effects of rapid infusion of essential fluids volume by hypotonic lactated Ringer's solution to mildly dehydrated heifers and to compare the central venous pressure (CVP) and acid-base equilibrium with isotonic lactated Ringer's or hypotonic Ringer's solution in order to determine their clinical usefulness.

MATERIALS AND METHODS

The experiments were performed on 9 Holstein breed heifers weighing 509.7 ± 44.9 kg. The heifers were deemed

healthy on the basis of physical examination, electrocardiography, and hematologic analysis. A complete, balanced diet consisting of pelleted concentrated feed and mixed grass hay was provided, and the heifers had unlimited access to fresh water and salt block (Koen E100: Nippon Zenyaku Kogyo Co., Ltd., Fukushima) until the start of the experiment.

Feed, salt block and water were withheld for 48 hr to induce dehydration. Before and at the end of the fasting, complete blood count (CBC), arterial gasses, serum electrolytes and plasma glucose concentration were determined. Approximately 1 hr before fluid infusion, 14-gauge catheters (IV catheter for animals: Nippon Zenyaku Kogyo Co., Ltd.) were implanted percutaneously into both jugular veins of the unanesthetized, conscious heifers. The catheter in the right jugular vein was connected via an ordinary drip tube [18–20] to a pump (ABP-101: Asahi Medical Co., Ltd, Tokyo) that controlled the flow rate. The catheter in the left jugular vein was used for the collection of venous blood samples. Furthermore, the catheter in the left jugular vein was connected to a strain-gauge transducer (Model DX-360: Nihon Koden Co. Tokyo) coupled to a galvanometric recorder (BP-308ETI: Nihon Koden Co.). Heart rate (HR) and rectal temperature (RT) were also monitored by use of a galvanometric recorder throughout the experimental period.

After preparations were completed, heifers were monitored for 15 min to ensure hemodynamic stability. The following commercial fluids were used: lactated Ringer's + 5% dextrose (ILG), 1/2 lactated Ringer's + 2.2% dextrose (HLG) and 1/2 Ringer's + 2.5% dextrose (HRG). Table 1 shows the compositions of the fluids used. The heifers were randomly assigned to the ILG (n=3; IV infusion of ILG), HLG (n=3; IV infusion of HLG) or HRG groups (n=3; IV infusion of IRG). Heifers received 30 ml/kg of one of the fluids, at a flow rate of 20 ml/kg/hr [16–18]. The initiation of the infusion of the fluid was designated as time 0. Venous blood samples were collected at time 0 (pre-infusion), 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min after initiation of fluid infusion. Immediately before collection of each blood sample, HR, CVP and RT were recorded. Venous samples were collected aerobically in heparinized 1-ml syringes, and the tips of syringes were capped after collection. Immediately after collection, blood samples were analyzed for pH and blood gasses by an automatic gas analyzer (model 248; Ciba-Corning Diagnostic Co, Essex,

UK) at 37°C. Values were automatically corrected to correspond to each heifer's RT. Some venous blood samples were used to determine hemoglobin concentrations (Hb) and hematocrit values (Ht); these samples were then stored in test tubes. Other blood samples were centrifuged, and plasma was collected and stored at –20°C until assayed.

Changes in relative plasma volume (rPV) were calculated from Hb and Ht, using accepted formulas [7, 17, 18]. The concentrations of sodium, potassium and chloride in the plasma were analyzed by electrode methods, using an automatic analyzer (model 644; Ciba-Corning Diagnostic). Plasma osmotic pressure was determined by the freezing point depression method (One-Ten osmometer, Fiske Association, Norwood, MA, U.S.A.). The plasma glucose and total calcium (Ca) concentrations were determined by glucose oxidation and o-cresolphthalein methods, respectively, using a clinical system (Synchron CX4 delta, Beckman Coulter Inc., CA, U.S.A.). The plasma DL-lactate concentration was determined by high performance liquid chromatography (L-4250, Hitachi, Ltd., Tokyo) using a fatty acid labeling kit (YMC Co., Ltd. Kyoto) [14].

Data are shown as mean \pm standard deviation. The effect of fasting was analyzed, using paired Student's *t*-test. Data were analyzed, using repeated-measures ANOVA. The variables included in the model were time, fluid infusion, and interaction of time and fluid infusion. Differences were considered significant at $P < 0.05$.

RESULTS

All heifers were clinically normal before the experiment, as determined on the basis of vital signs, attributes, food and water intake, and urine and feces production. Dryness and chilliness of oral mucous membrane, sinking of the eyes, and eyelid skin tenting of about 0.5 sec were the main clinical signs following fasting.

The pre-fasting values of HR, venous pH, and plasma DL-lactate, glucose, sodium and osmolality were 54.6 ± 6.0 bpm, 7.392 ± 0.022 , 2.0 ± 0.9 mM, 71.1 ± 6.8 mg/dl, 137.8 ± 0.7 mM and 281.1 ± 1.6 mOsmol/l, respectively. Fasting for 48 hr induced significant decreases in HR (45.3 ± 5.5 bpm, $P < 0.001$), pH (7.357 ± 0.019 , $P < 0.01$) and glucose (60.2 ± 8.4 mg/dl, $P < 0.01$), and significant increases in DL-lactate (3.1 ± 1.2 mM, $P < 0.01$), sodium (142.1 ± 1.7 mM, $P < 0.001$) and osmolality (288.9 ± 4.0 mOsmol/l, $P < 0.001$).

Table 1. Composition of the hypotonic fluids used in this study

	Na ⁺ (mEq/l)	K ⁺ (mEq/l)	Ca ⁺⁺ (mEq/l)	Cl ⁻ (mEq/l)	Lactate (mEq/l)	Glucose (mg/dl)	Osmolality (mOsmol/l)
ILG	130.0	4.0	3.0	109.0	28.0	5.0	525.0
HLG	65.5	2.0	1.5	55.0	28.0	2.2	280.0
HRG	73.5	2.0	2.5	78.0	–	2.5	284.0

ILG: Lactated Ringer's solution with 5.0% dextrose (Harutou-V injection: Nippon Zenyaku Kogyo Co., Ltd.). HLG: Hypotonic lactated Ringer's solution with 2.2% dextrose (Touchou haruzentou-V injection: Nippon Zenyaku Kogyo Co., Ltd.). HRG: Hypotonic Ringer's solution with 2.5% dextrose (Touchou ringerutou-V injection: Nippon Zenyaku Kogyo Co., Ltd.).

The average decrease of rPV, calculated by the Hb and Ht determinations, was $7.0 \pm 5.7\%$. Plasma bicarbonate, base excess (BE), Ca, potassium and chloride concentrations did not significantly differ from the samples obtained before and after fasting.

Clinical signs, such as moist rales on auscultation, moist cough, jugular vein congestion, ophthalmoptosis, salivation or arrhythmia, were not observed throughout the fluid infusion. HR was not changed by fluid infusion and remained constant throughout the experimental period for all the groups. Sequential change in CVP was monitored in dehydrated heifers (Fig. 1). ILG infusion induced progressive and significant increases in CVP, which reached 9.0 ± 2.0 mmHg at 30 min after initiation of fluid infusion, and then was maintained between 8.0 and 9.0 mmHg throughout the fluid infusion ($P < 0.05$ vs pre-infusion, by ANOVA). For the HLG and HRG groups, CVP values increased slightly at the end of the fluid infusion, reaching 3.7 ± 1.2 and 4.0 ± 0.0 mmHg, respectively, but these variables were not significant between the groups. The sequential change of CVP for the ILG group was significantly greater than those for the other groups ($p < 0.05$). Figure 2 shows the relative changes in plasma volume (rPV) in heifers given fluid infusion. The rPV of the HLG and HRG increased progressively and exceeded the pre-fasting values, reaching $121.4 \pm 7.8\%$ and $126.9 \pm 7.4\%$, respectively. The expanded plasma volume of both groups remained up to 5% higher than the pre-fasting level for the entire 360 min. The rPV of the ILG group increased markedly until the end of the fluid infusion ($136.5 \pm 14.4\%$), compared with other groups ($P < 0.05$ by ANOVA).

The pre-infusion values for venous pH in the ILG, HLG

and HRG groups were 7.368 ± 0.014 , 7.361 ± 0.019 and 7.347 ± 0.023 , respectively. The start of ILG or HRG infusion induced significant decreases in pH. The pH of the ILG group then returned to the pre-infusion levels, however, the pH of the HRG group remained low throughout the remainder of the monitoring periods. In contrast, the pH of the HLG group did not significantly change throughout the experiment. Figure 3 shows the relative changes in BE (rBE) in heifers given fluid infusion. The rBEs of the ILG and HRG groups were significantly decreased compared to the pre-infusion values until the end of the fluid infusion, reaching -3.7 ± 1.1 and -3.4 ± 1.1 mM, respectively. There was an increase in the rBE of the HRG group after the end of fluid infusion, and it returned to the pre-infusion levels at 300 min after the initiation of the fluid infusion. In contrast, rBE of ILG group after the fluid infusion had stopped significantly increased and exceeded the pre-infusion values, reaching 1.9 ± 1.6 mM at the end of the experiment. For the HLG group, rBE decreased slightly until the end of the fluid infusion, and thereafter increased significantly and exceeded the pre-infusion value, reaching 1.7 ± 0.5 mM at the end of the experiment. Sequential changes of pH and rBE values for the HLG group were significantly greater than those for the other groups ($P < 0.05$).

Sequential changes in plasma DL-lactate and glucose concentrations were monitored in the dehydrated heifers. The pre-infusion values for the plasma DL-lactate concentrations in the ILG, HLG and HRG groups were 2.68 ± 0.65 , 3.89 ± 0.85 and 3.76 ± 0.34 mM, respectively. The DL-lactate concentration was significantly decreased after the infusion of HRG, reaching 2.17 ± 0.23 mM at the end of HRG infusion ($P < 0.05$ by ANOVA). Infusion of ILG and HLG

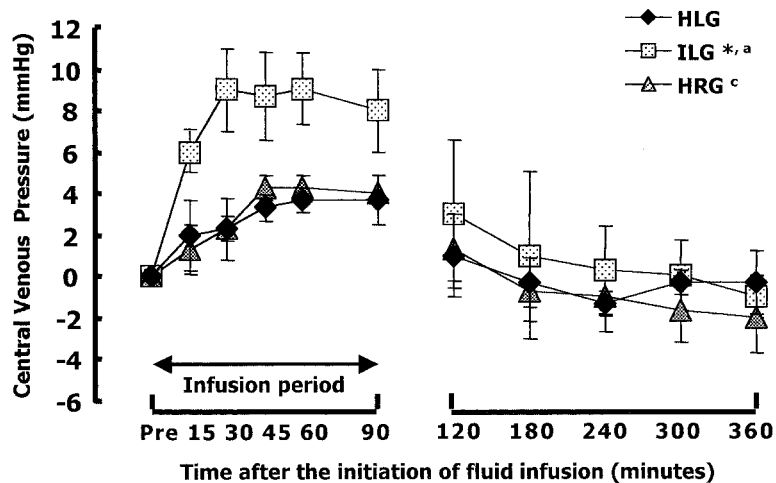


Fig. 1. Graphs depicting the central venous pressure (CVP) in dehydrated heifers administered hypotonic fluid. ILG: lactated Ringer's solution with 5.0% dextrose, HLG: 1/2 lactated Ringer's solution with 2.2% dextrose and HRG: 1/2 Ringer's solution with 2.5% dextrose. Levels of significance ($p < 0.05$) indicated: a: HLG versus ILG, b: HLG versus HRG, c: ILG versus HRG, and asterisk: versus pre-infusion values by ANOVA.

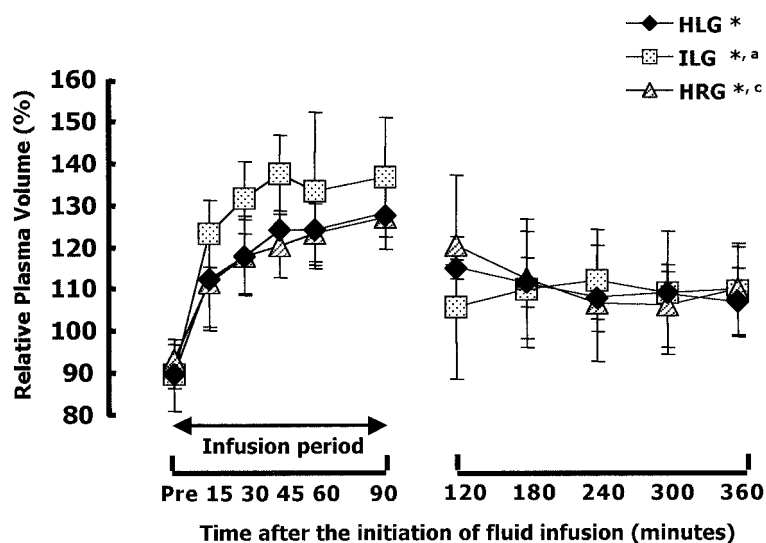


Fig. 2 Graphs depicting the relative plasma volume (rPV) in dehydrated heifers administered hypotonic fluid. See Fig. 1 for key.

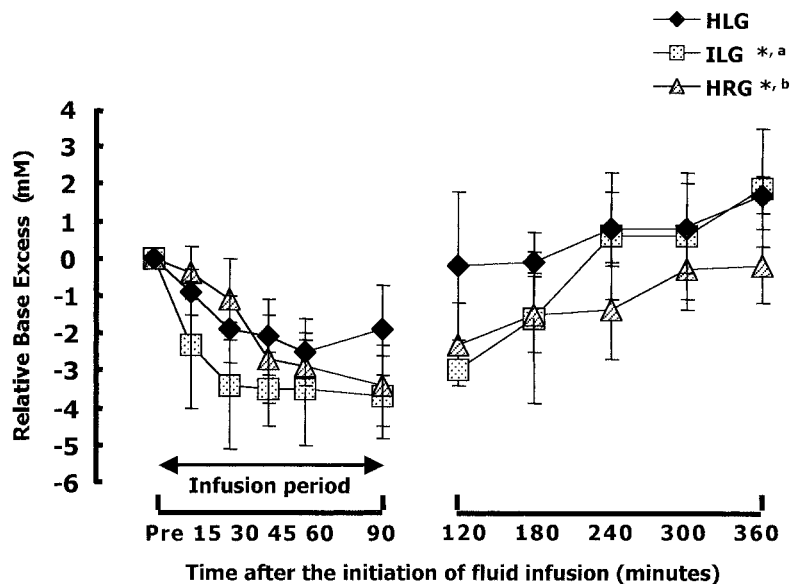


Fig. 3 Graphs depicting the relative base-excess (rBE) in dehydrated heifers administered hypotonic fluid. See Fig. 1 for key.

induced a significant increase in the plasma DL-lactate concentrations during the fluid infusion period, but thereafter they remained at the pre-infusion values ($P < 0.05$ by ANOVA). The pre-infusion values of plasma glucose in the ILG, HLG and HRG were 69.0 ± 1.7 , 61.3 ± 0.6 and 50.3 ± 4.0 mg/dl, respectively. Significant increases in plasma glucose concentration were induced in heifers by HLG or HRG infusion, reaching 345.0 ± 32.8 and 362.0 ± 15.0 mg/dl at the end of infusion, respectively ($P < 0.05$ by ANOVA). ILG infusion induced marked and significant increases in plasma

glucose concentration, compared with the other groups (691.1 ± 47.6 mg/dl at the end of the fluid infusion, $P < 0.05$). For all the groups, plasma sodium, potassium and chloride concentrations decreased until the end of fluid infusion, but not significantly and they were not significantly different among the 3 groups. Plasma osmotic pressure was not affected by HLG or HRG infusion and remained constant throughout the experimental period. However, plasma osmotic pressure for the ILG group was progressively and significantly increased until the end of fluid infusion (310.7

± 6.5 mOsmol/l), then returned to the pre-infusion value ($P < 0.05$). No significant differences were observed in the plasma calcium concentration among the 3 groups.

DISCUSSION

The rapid (20 ml/kg/hr) IV infusions of HLG and HRG used in this study were found to be safe and effective in increasing plasma volume without increasing CVP, even though the infusion was given to the jugular vein at a dosage of 30 ml/kg. While IV infusion of HLG inhibited acidification caused by dilution, HRG infusion induced diluted acidification. It is suggested that HLG infusion should be explored as a treatment for cattle with dehydration and moderate metabolic acidosis, since rapid infusion of HLG may be more beneficial for rehydrating cattle with metabolic acidosis more than conventional treatment.

For hydrating dehydrated cattle, the fluid requirement is calculated to rectify the deficiency and to supply an additional 30 ml/kg to compensate for essential water losses. For example, if the water deficiency and essential water were calculated at 5% (=50 ml/kg) and 30 ml/kg [17, 19–21], the recommended fluid requirement is 80 ml/kg. In practical applications of fluid therapy, however, time, labor and expense of treatment severely limit the replacement volume [19–21]. Therefore, it is considered that essential water loss (=30 ml/kg) is a suitable minimum volume for fluid therapy in cattle practice [17]. The rate of fluid administration should not exceed 40 ml/kg/hr [2, 9]. This means that a maximum fluid volume of 24 l for 600 kg/hr for dehydrated cattle can be administered. A previous study showed that a flow rate of about 17.8 ± 1.9 ml/kg/hr for cattle was maximal with a 14-gauge catheter and drip tube as standard equipment in clinical practice [17]. Therefore, we suggest that a rate of 20 ml/kg/hr is a good choice for rapid administration of fluid to cattle weighing more than 300 kg.

Telltale signs indicate that the infusion rate or volume given is excessive. These signs include the development of moist rales on auscultation and the presence of a moist cough or a serous nasal discharge [13]. Venous congestion, especially of the jugular vein and a sustained rise of CVP to 4.414 mmHg should also be taken as signs that the infusion rate or the volume given is excessive [5, 12]. In this study, the IV infusion of 30 ml/kg of hypotonic fluids, at a flow rate of 20 ml/kg/hr, did not induce any abnormal clinical signs caused by plasma expansion. For the HLG and HRG groups, CVP values were slightly increases at the end of the fluid infusion, reaching 3.7 ± 1.2 and 4.0 ± 0.0 mmHg, respectively, but these variables were not significant. The increase in CVP of both hypotonic solutions was less than 4.414 mmHg during the infusion. In contrast, ILG infusion induced progressive and significant increases in CVP, reaching 9.0 ± 2.0 mmHg at 30 min after initiation of fluid infusion, and then remained between 8.0 and 9.0 mmHg throughout the fluid infusion. In the dehydrated heifers, the rPV for the HLG and HRG groups increased markedly during the fluid infusion, and the expanded plasma volume of

both groups remained up to 5% higher than the pre-fasting level after the end of fluid infusion. The ILG infusion induced marked and significant increases in rPV, because the ILG (an osmolality of 525 mOsmol/l) generates an osmotic plasma expansion and increases plasma volume by extracting water from cells. These results indicate that hypotonic fluid is advisable for dehydrated cattle. On the basis of these findings, it is suggested that 30 ml/kg of hypotonic solution at a flow rate of 20 ml/kg/hr can be safely infused into cattle.

Cattle, especially in early lactation, are often candidates for fluid therapy because they are at greatest risk to diseases that lead to dehydration and electrolyte imbalance caused by negative energy balance [2]. Therefore, it is often desirable to include glucose in intravenously administered solutions because glucose is used for energy [16]. The net effect of infusion of 5% glucose is to deliver free water. This results in dilution of electrolytes, seldom a desirable consequence [16, 17]. Furthermore, Persson *et al.* [15] suggested that hypotonic solution with 2.5% dextrose appeared to be able to correct dehydration in a short time, when it was used for treating for chronically dehydrated children with deficiency of intracellular fluids. Therefore, in practice for children [15], small animals [12] and cattle [17, 18], it is preferable to infuse 2.5 to 5.0% dextrose in 0.45 to 0.90% sodium chloride or other electrolyte solutions. Incidental hypoglycemia may occur as a rebound from hyperglycemia. The reabsorption rate of glucose in the kidney is approximately 0.5 g/kg/hr [17, 18], and an increase in blood insulin might cause a rebound phenomenon after fluid infusion containing dextrose. In this study, however, no hypoglycemia was observed in the HLG and HRG groups, and the flow rates of glucose contained in the HLG and HRG (20 ml/kg/hr) were about 0.48 and 0.50 g/kg/hr, respectively.

A large amount of HRG does not significantly correct base deficits in acidemia or in healthy calves [2, 9]. Solutions without an alkalinizing agent are, therefore, of limited use in cattle with metabolic acidosis [3]. Sodium bicarbonate should be used for the treatment of severe acidemia. Kasari and Naylor [9–11] reported that bicarbonate solution given IV to correct acidosis in calves effectively raised blood pH and BE. As a bicarbonate precursor, sodium acetate and lactate have similar alkalizing effects on blood [10]. Lactated Ringer's solution, such as Hartmann's solution, is by far the most versatile of the fluids generally used in small animal [5, 6] and cattle [4] practice. Lactate is present as a bicarbonate precursor to correct metabolic acidosis in lactated Ringer's solution in a concentration of 28 mEq/l [8]. HLG and ILG used in this study also contained a 28 mEq/l of sodium lactate. Slower onset of alkalization after infusion of sodium lactate is consistent with its metabolism prior to its effective buffer action [8]. In this study, the relative changes in BE for the ILG and HRG groups were significantly decreased until the end of the fluid infusion. There was an increase in the rBE of the HRG group, but it returned to the pre-infusion values at 300 min after the initiation of the fluid infusion. In contrast, rBE of the HLG group

increased significantly after the fluid infusion and exceeded the pre-infusion values.

To determine the effects of rapid infusion of essential fluids volume of HLG to mildly dehydrated heifers, an experimental model for dehydration of cattle is desirable. Mild dehydration was induced by withholding food and water for dogs [3] and cattle [17]. Cornelius *et al.* [5] reported that mild dehydration was produced in the dog by withholding food and water for 3 or 4 days. For cattle, the decrease of mean body weight from fasting for 48 hr was approximately 7.7% [17]. Therefore, that model of fasting met our experimental requirements for mild dehydration in heifers.

In the study reported here, initiation of HLG, HRG or ILG infusion after 48 hr of fasting was designed as $t=0$. Initially, a simple paired test of values obtained before (pre-fasting) and after fasting, ignoring treatment group, was used to determine variables that would be affected by fasting. Repeated measures ANOVA was used for all variables of interest, using pre-infusion values for comparison, to detect treatment effect. The results suggested that hypotonic fluids with 28 mEq/l of sodium lactate could be used to correct less severe metabolic acidosis in the dehydrated cattle. Therefore, IV infusion of a HLG should be examined as a treatment for dehydration and moderate metabolic acidemia in cattle. Although it is doubtful whether a sufficient fluid volume to meet the animal's requirement is being given in clinical practice, on the basis of the findings in this study, 30 ml/kg of hypotonic solution at a flow rate of 20 ml/kg/hr can be safely infused into cattle. In fact, the infusion of HLG may be more beneficial than that of HRG for rehydrating cattle with metabolic acidosis. Additional studies are needed before definitive recommendations can be made regarding the optimal fluid to use for rehydration and correction of moderate acidemia in cattle.

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