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Intravenous polyionic solution with a high concentration of lactate (84 mEq/L) is effective for the treatment of diarrheal calves

[*Solução intravenosa poliiônica com concentração elevada de lactato (84 mEq/L) é eficaz para o tratamento de bezerros com diarreia*]

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ABSTRACT

This study aimed to evaluate the effectiveness of an electrolyte solution with a high lactate concentration (84mEq/L; L84) in correcting imbalances in diarrheal calves. Another solution with similar electrolyte composition, containing 84mEq/L of bicarbonate (B84) was used for comparison. Diarrhea was induced in neonatal calves by rotavirus infection, sucrose ingestion and furosemide administration. When a moderate degree of metabolic acidosis was reached, the calves were treated with intravenous infusion of L84 (n=10) or B84 (n=10) solutions. Venous blood and urine samples were collected before starting the infusion (0 h), in the middle (2.5 h), at the end (5.0 h) and 2.5 hours later. Total plasma protein concentration, blood and urine pH, blood pCO_2, HCO_3^-, and BE, plasma and urine concentration of L-lactate, and serum and urine concentrations of Na^+, K^+, and Cl^- were measured. Strong ion difference, total concentration of non-volatile weak acids, anion gap, strong ion gap, percentage change in plasma volume, and urinary fractional clearances of Na^+, K^+, Cl^-, and L-lactate were calculated. The calves demonstrated moderate dehydration, hypernatremia, hyperchloremia, metabolic acidosis, and unmeasured anion accumulation. These changes were completely corrected with the L84 solution, and the effects did not differ from those observed with B84 solution. The calves recovered without further therapeutic procedures, demonstrating that the L84 solution was effective for treating diarrheal calves.

Keywords: neonatal diarrhea, metabolic acidosis, dehydration, fluid therapy, electrolyte solution

RESUMO

O objetivo deste estudo foi avaliar a eficácia de uma solução eletrolítica com concentração elevada de lactato (84 mEq/L; L84) para corrigir os desequilíbrios em bezerros diarreicos. Outra solução com composição eletrolítica similar, contendo 84 mEq/L de bicarbonato (B84), foi utilizada para comparação. Diarreia foi induzida em bezerros neonatos por infecção com rotavírus, ingestão de sacarose e administração de furosemida. Quando o grau moderado de acidose metabólica foi alcançado, os bezerros foram tratados com as soluções intravenosas L84 (n=10) ou B84 (n=10). Amostras de sangue venoso e de urina foram colhidas antes de iniciar a infusão (0 h), na metade (2,5 h), ao término (5,0 h) e 2,5 horas após. Determinaram-se proteína plasmática total, pH sanguíneo e urinário, pCO_2, HCO_3^- e BE sanguíneos, concentração plasmática e urinária de lactato L e concentrações séricas e urinárias de Na^+, K^+ e Cl^-. Calcularam-se a diferença de íons fortes, a concentração de ácidos fracos não voláteis, o hiato aniônico, o hiato de íons fortes, a variação percentual do volume plasmático e as excreções fracionadas urinárias de Na^+, K^+, Cl^- e lactato L. Os bezerros apresentaram desidratação moderada, hipernatremia, hipercloremia, acidose metabólica e acúmulo de ânions não mensurados. Essas alterações foram completamente corrigidas com a solução L84, e os efeitos não diferiram dos observados com a solução B84. Os bezerros se recuperaram sem outros procedimentos terapêuticos, comprovando que a solução L84 é eficaz para o tratamento de bezerros diarreicos.

Palavras-chave: diarreia neonatal, acidose metabólica, desidratação, terapia com fluidos, solução eletrolítica

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INTRODUCTION

Acute diarrhea in newborn calves can be caused by different viral, bacterial, or protozoan enteropathogens, in single or mixed infections, and is considered the main health problem for these animals in the first weeks of life worldwide (Smith, 2012; Windeyer *et al.*, 2014). Regardless of the causative agent, it causes water, electrolyte and acid-base imbalances that can vary in intensity and are characterized by dehydration, hyponatremia, relative hyperchloremia, potassium depletion, hyper-D-lactatemia, and metabolic acidosis (Gomez *et al.*, 2017; Trefz *et al.*, 2017). The preservation of the lives of diarrheal calves depends, therefore, on the replacement of fluids and electrolytes and on the correction of metabolic acidosis (Smith and Berchtold, 2014; Constable *et al*., 2021).

Among the electrolyte solutions for intravenous use available in the Brazilian market, lactated Ringer's solution (LRS) can be identified as the only one with alkalizing capacity. The other solutions have an effective strong ion difference ($SID_{3\ effective}$) equal to 0 mmol/L and are, for this reason, acidifying (Constable, 2014; Constable *et al.*, 2021), while the LRS has a $SID_{3\ effective}$ equal to 28 mmol/L, equivalent to the concentration of $lactate^-$ in the solution. The LRS would therefore be the appropriate commercial choice for intravenous fluid therapy of diarrheal calves. However, its alkalizing potential has not been confirmed in healthy calves (Cosenza *et al.*, 2013; Junqueira *et al.*, 2015), sheep (Flaiban *et al.*, 2009; Cosenza *et al.*, 2013), goats (Pereira *et al.*, 2021), and horses (Cosenza *et al.*, 2013), and this solution did not correct metabolic acidosis in ewes affected by acute rumen lactic acidosis (ARLA) (Cosenza *et al.*, 2015).

Taking the electrolyte composition of the LRS as a basis, a new intravenous polyionic solution was devised by reducing the concentration of chlorides (Cl^-) to 53mEq/L and tripling the concentration of $lactate^-$ (L84). This solution has a $SID_{3\ effective}$ equal to 84mEq/L, and this gives it a much greater alkalizing property. Its high alkalinization potential has been proven in healthy calves (Junqueira *et al*., 2015), sheep (Flaiban *et al.*, 2009), goats (Pereira *et al.*, 2021), and horses (Pinto *et al.*, 2018). Its effectiveness to correct metabolic acidosis has been proven in sheep (Flaiban, 2010) and goats (Pereira *et al.*, 2022) with ARLA, and horses with hyperchloremic acidosis (Romão *et al.*, 2015). In these studies with ruminant species, the iatrogenic effects of the L84 solution did not differ from the effects of an electrolyte solution with equivalent concentration of bicarbonate ion instead of $lactate^-$ (B84).

Based on previous observations in healthy calves and in ruminants and horses with metabolic acidosis, the authors hypothesized that the intravenous administration of the L84 solution would be able to correct dehydration and metabolic acidosis in calves affected by diarrhea, without differing from the B84 solution. This study aimed to evaluate whether an intravenous polyionic solution containing 84 mEq/L of lactate is effective in correcting water, electrolyte and acid-base imbalances present in diarrheal newborn calves.

MATERIAL AND METHODS

This was a randomized controlled trial with a repeated measures design previously approved by the Ethics Committee on Animal Experimentation at the Universidade Estadual de Londrina (CEEA/UEL; protocol 26/06).

The electrolyte solution with a high concentration of sodium lactate (L84) used in the present study was designed based on the commercial lactated Ringer's solution (LRS). The concentrations of sodium (130mEq/L), potassium (4mEq/L), and calcium (3mEq/L) and the calculated osmolarity (275mOsm/L) of the LRS were maintained. The lactate concentration was tripled (84mEq/L) and the chloride concentration was decreased (53mEq/L). Another solution with a similar composition (B84) containing bicarbonate (84mEq/L) instead of lactate, lacking in calcium and with a calculated osmolarity of 272mOsm/L, was used, serving as a standard for comparison.

The solutions were prepared shortly before administration, using commercially sterilized double-distilled water (1,000mL bottles) (Água para injetáveis, Indústria Farmacêutica Texon Ltda., Viamão, RS, Brazil). The components used for the preparation were: NaCl, KCl, $CaCl_2$, and sodium lactate or $NaHCO_3$ (Synth, Labsynth Produtos para Laboratórios, Diadema, SP, Brazil).

Twenty clinically healthy Girolando calves (12 males and 8 females), with 46.2±5.7kg of body weight (BW), between 9 and 30 days old (15±5 days) were used. The calves originated from eutocic births and non-twin pregnancies. During the entire experimental period, the calves were kept in individual pens and were fed 2L of whole milk twice a day, with free access to water and coast-cross grass hay (*Cynodon dactylon*).

Diarrhea was induced through oral infection with the rotavirus NCDV (Nebraska calf diarrhea virus): 2mL of an inoculum with an infective dose of 10^6 $TCID_{50}$/mL, in a single dose. Inoculums were preserved by freezing in liquid nitrogen until infection. Thawing was performed in a water bath at 56ºC, and the inoculum was previously activated with 10 μg of trypsin. From the day after the infection, the calves began to receive sucrose (Açúcar Cristal Alto Alegre, Usina Alto Alegre, Presidente Prudente, SP, Brazil), at a dose of 4g/kg BW, diluted in the milk at each feeding, and a daily dose of 1mg/kg BW of furosemide (Semidin®, FAGRA – Farmagrícola SA, Mairiporã, SP, Brazil), intramuscularly. This protocol was maintained until the desired degree of metabolic acidosis was reached (BE ≤ –8.0 mmol/L). To assess the degree of acidosis present, daily analyzes of blood gases were performed on venous blood samples, starting on the third day after infection. The collection was always carried out in the morning, before the first feeding.

Calves were randomly allocated into two treatment groups (n=10): intravenous infusion with L84 solution or with B84 solution. The infusion was performed in the auricular vein using a 22G catheter for 5 h of continuous administration, at a rate of 25mL/kg/h (approximately 1L/h), totaling a volume of 5L. The ingestion of sucrose and the administration of furosemide were suspended, and the first feeding of the day occurred only 2.5 h after the end of the infusion. The calves remained under constant observation throughout the duration of the infusion to detect possible manifestations that characterized side effects and physical examinations were performed at the beginning and at the end of the infusion.

Venous blood samples were collected by puncturing the jugular vein at four times: before the start of the infusion (0 h), in the middle of the infusion (2.5h), at the end of the infusion (5h) and 2.5 h after the end of the infusion (7.5h). The blood samples were placed in vacuum flasks containing EDTA anticoagulant for the measurement of total plasma protein (TP), in flasks containing EDTA and sodium fluoride for the measurement of L-lactate, in flasks without anticoagulant for the measurement of creatinine, and in heparinized syringes for blood gas analysis. Fluoridated plasma was obtained after centrifugation performed within a maximum of 15 minutes after collection, and serum was obtained by centrifugation after clot retraction. Serum and plasma were preserved by freezing (-20°C) until analysis. Blood gas analysis was performed shortly after collection.

Urine samples were obtained by preputial massage in males and perineal massage in females, at the same time as blood collection. Urine pH and specific gravity were measured shortly after collection. The other measurements were later performed on the samples preserved by freezing (-20°C).

In venous blood samples, pH, carbon dioxide partial pressure (pCO_2), bicarbonate concentration (HCO_3^-), base excess (BE), sodium (Na^+), potassium (K^+), and chloride (Cl^-) were measured (Omni C, Roche Diagnóstica, São Paulo, SP, Brazil). TP concentration and urine specific gravity were measured by refractometry (Refratômetro Atago, Atago Brasil Ltda., Ribeirão Preto, SP, Brazil). L-lactate concentrations in plasma and urine were measured by the enzymatic method (Lactato, Bioclin-Quibasa, Belo Horizonte, MG, Brazil) with spectrophotometric reading (Espectrofotômetro Bioplus 2000, Bioplus Produtos para Laboratórios, Barueri, SP, Brazil). Creatinine concentrations in serum and urine were measured by the kinetic method (Creatinina, Bioclin-Quibasa, Belo Horizonte, MG, Brazil) with spectrophotometric reading. Urine concentrations of Na^+, K^+, and Cl^- were measured using the ion-selective electrode method (Dimension Clinical Chemistry System, Dade Behring, Siemens Healthcare Diagnostics SA, São Paulo, SP, Brazil). Urine pH was measured with an electronic potentiometer (pHmetro Analion, Analion Aparelhos e Sensores, Ribeirão Preto, SP, Brazil).

The following variables were calculated using the corresponding formulas:

- Anion gap (AG): AG= $(Na^+ + K^+) - (Cl^- + HCO_3^-)$
- Strong Ion Difference (SID_3): $SID_3 = (Na^+ + K^+) - Cl^-$
- Total plasma concentration of non-volatile weak acids (A_{tot}): A_{tot} = TP (g/dL) × 3.43 (Constable *et al.*, 2005)
- Strong ion gap (SIG): SIG = $[A_{tot}/(1+10^{(7.08 - pH)})]$ – AG (Constable *et al.*, 2005)
- Fractional clearance (FC) of electrolytes and L-lactate (Garry *et al.*, 1990):

FC (a) = (urine concentration of (a) × plasma creatinine/plasma concentration of (a) × urine creatinine) × 100
where (a) is the excreted substance.
- Percentage change in plasma volume (%PV): %PV = $[(TP_1/TP_2) - 1] \times 100$ (Carlson and Bruss, 2008)
where TP_1 is the TP value observed before treatment (0 h) and TP_2 is the TP values of the subsequent time points.

For the purpose of interpreting the results, the following reference ranges were considered:
pH (7.35 – 7.50), pCO_2 (34 – 45 mmHg), HCO_3^- (20 – 30 mmol/L), BE (0 – 6mmol/L), Na^+ (132 – 152 mmol/L), K^+ (3.9 – 5.8 mmol/L), Cl^- (95 – 110 mmol/L), SID_3 (approximately 40 mmol/L), AG (14 – 20 mmol/L), TP (5.7 – 7.5 g/dL), A_{tot} (19 – 25 mmol/L), L-lactate (< 1.5 mmol/L), and SIG (–5 – +5 mmol/L) (Constable *et al.*, 2005; Radostits *et al.*, 2007; Constable, 2014).

The Shapiro-Wilk and Brown-Forsythe tests were used to verify the Gaussian distribution and equality of variance, respectively. One-way repeated measures ANOVA was used to assess the effect of each infused solution over time. Tukey's test was used for multiple comparisons. Comparison between the two solutions at each time point was performed using the unpaired t-test. In the case of FC of electrolytes and L-lactate, Friedman's repeated measures ANOVA was used considering each solution separately, and the Mann-Whitney test was used to compare the solutions at each time point. A probability error of 5% was assumed. SigmaPlot for Windows 13.0 (Systat Software Inc., San Jose, California, USA) was used to perform the statistical analysis.

RESULTS

The calves started diarrhea the day after the induced infection. The feces remained light yellow in color, had a slightly unpleasant odor, and varied in consistency from pasty, at the beginning, to liquid from the third day onwards. Dehydration gradually increased during evolution and all calves reached a moderate to accentuated degree of imbalance, estimated at 10% BW, and characterized by mild lethargy, enophthalmos (4 to 6 mm), and reduced skin elasticity (2 to 5 seconds). On the day the calves were treated, BW had decreased by 6.4±1.9kg (L84) and 6.4±2.5kg (B84) (P = 0.993), which is equivalent to a 13.8±4.8% reduction in BW, without distinction between groups (P = 0.929). Even dehydrated, calves maintained normal appetite, present and vigorous sucking reflex, and did not adopt the permanent recumbency. Moderate-intensity metabolic acidosis (BE≤–8.0 mmol/L) was reached from the third to the eighth day of evolution (6.2±1.6 days) without distinction between groups (P = 0.812).

Treatment with the L84 solution resulted in an increase in the values of blod pH (P < 0.001), HCO_3^- (P < 0.001), BE (P < 0.001), SID_3 (P < 0.001), SIG (P < 0.001), and %PV (P < 0.001), and in a decrease in the values of Na^+ (P < 0.001), K^+ (P < 0.001), Cl^- (P < 0.001), AG (P < 0.001), TP (P < 0.001), and A_{tot} (P < 0.001). These changes were maintained after the end of the infusion (7.5 h) for most studied variables (Table 1 and Fig. 1 and 2). L-lactate concentration increased (P < 0.001) until the end of the intravenous infusion and returned to baseline values later (7.5 h). pCO_2 values fluctuated during the infusion and increased after completion (P = 0.031). In urine, pH (P<0.001) and the FC of Na^+ (P<0.001), K^+ (P < 0.001), and Cl^- (P<0.001) increased, specific gravity decreased (P < 0.001), and the FC of L-lactate fluctuated slightly (P < 0.017) (Table 2).

The infusion of B84 solution caused changes similar to this over time and few differences were observed between treatments (Tab. 1 and 2 and Fig. 1 and 2). The pCO_2 was higher in the L84 treatment after the end of the infusion (7.5 h) and the HCO_3^- and BE values were higher

with B84 solution in the middle of the infusion (2.5 h) and with L84 solution after the end of the infusion (7.5 h). The plasma concentration of L-lactate did not change with the infusion of the B84 solution, which differed ($P < 0.001$) from the treatment with the L84 solution in the middle and at the end of the infusion. After completion, concentrations were the same in both treatments (Table 1 and Fig. 2).

All calves recovered completely and intravenous administration of L84 or B84 solutions was the only therapeutic procedure they were submitted to. Feces gradually returned to normal consistency and all calves were clinically healthy 2 to 4 days after treatment.

DISCUSSION

The protocol used for the experimental induction of diarrhea, dehydration, and metabolic acidosis was successful and all calves started diarrhea the day after the infection. The association between rotavirus infection and sucrose ingestion ensured the occurrence and maintenance of diarrhea until the desired degree of metabolic acidosis was reached. The administration of furosemide probably contributed to accentuating the degree of dehydration. Based on the approximately 14% BW reduction, dehydration could be classified as severe. However, the degree of enophthalmos, the decrease in skin elasticity, behavior, and posture indicate that the calves showed estimated dehydration close to 10% BW, which marks the limit between moderate and severe dehydration (Smith, 2009). Elevated initial values of TP, A_{tot}, and urine specific gravity characterize hemoconcentration and concentrated urine output and are reliable indicators of the water imbalance that calves have developed. The low baseline values of blood pH, HCO_3^-, and BE and urine pH confirm that the calves showed uncompensated metabolic acidosis (DiBartola, 2012; Constable, 2014) of moderate intensity (Izzo *et al.*, 2015).

Electrolyte imbalances were characterized by mild hypernatremia and hyperchloremia, with no change in plasma SID_3 and K^+ concentration, which indicates that the calves did not have hyperchloremic metabolic acidosis. On the contrary, the high AG and low SIG baseline values indicate that the metabolic acidosis was caused by the accumulation of organic acids (unmeasured anions), including D-lactate (Constable *et al.*, 2005; Gomez *et al.*, 2017; Trefz *et al.*, 2017). These results partially contradict those observed in previous studies of induction of osmotic diarrhea and dehydration in newborn calves using a protocol with diluted sucrose mixed with milk and with diuretics spironolactone and hydrochlorothiazide, in which metabolic acidosis was mild (Leal *et al.*, 2008, 2012) or hyponatremia, relative hyperchloremia, and reduced plasma SID_3 were the changes responsible for metabolic acidosis (Bregadioli *et al.*, 2022, 2023). The distinctions between the induction protocols used, notably the infection with rotavirus and the prolonged time of sucrose ingestion, may explain the differences observed in the results.

The electrolyte and acid-base imbalances that the studied calves demonstrated are consistent with those seen in natural cases of neonatal diarrhea (Gomez *et al.*, 2017; Trefz *et al.*, 2017). Hyper-D-lactatemia, resulting from the absorption of D-lactate synthesized by the microbiota on the large intestine, is currently considered the most important cause of metabolic acidosis in diarrheal newborn calves (Lorenz and Gentile, 2014; Constable *et al.*, 2021). Plasma D-lactate concentration was not measured in the studied calves, but judging by the low SIG baseline values, it is consistent to assume that D-lactate concentration was increased.

Intravenous administration of the L84 solution was effective in correcting dehydration and electrolyte and acid-base imbalances in the calves. The infused volume of 5 L represented a volume corresponding to 12.5% of the BW on average, which is slightly greater than what is necessary to reverse dehydration estimated at 10% of the BW. At the end of the infusion, the increase in plasma volume was accompanied by a decrease in the values of TP, A_{tot}, K^+, AG, SIG, and urine specific gravity, characterizing the correction of hemoconcentration and the elimination of less concentrated urine. These results are consistent with previous observations in which the L84 solution was infused in healthy calves (Junqueira *et al.*, 2015), ewes (Flaiban *et al.*, 2009), horses (Pinto *et al.*, 2018), and goats (Pereira *et al.*, 2021), as well as in dehydrated sheep (Flaiban, 2010) and goats (Pereira *et al.*, 2022) affected by ARLA.

Table 1. Venous blood or plasma values (mean ± SD) of pH, pCO_2, HCO_3^-, BE, Na^+, K^+, Cl^-, strong ion difference (SID_3), anion gap (AG), total protein (TP), total concentration of non-volatile weak acids (A_{tot}), L-lactate, strong ion gap (SIG), and percentage change in plasma volume (%PV) of acidotic diarrheal calves before the beginning (0 h), in the middle (2.5 h), at the end (5 h) and 2.5 hours after the end (7.5 h) of the intravenous infusion of polyionic solutions (PS) containing 84 mEq/L of lactate (L84; n = 10) or 84 mEq/L of bicarbonate (B84; n = 10)

Variable	PS	0 h	2.5 h	5 h	7.5 h
pH	L84	7.219^{Ac}±0.044	7.362^{Ab}±0.028	7.434^{Aa}±0.024	7.444^{Aa}±0.039
	B84	7.231^{Ac}±0.069	7.391^{Ab}±0.056	7.444^{Aa}±0.037	7.433^{Aa}±0.035
pCO_2 (mmHg)	L84	42.86^{Aab}±6.19	41.51^{Ab}±3.19	45.73^{Aab}±3.11	47.64^{Aa}±5.48
	B84	40.75^{Aa}±6.60	44.60^{Aa}±7.13	44.28^{Aa}±4.95	42.86^{Ba}±3.69
HCO_3^- (mmol/L)	L84	17.03^{Ac}±1.74	23.11^{Bb}±2.17	30.16^{Aa}±2.16	31.91^{Aa}±3.19
	B84	16.61^{Ac}±1.72	26.48^{Ab}±4.62	29.62^{Aa}±2.60	28.05^{Bab}±2.57
BE (mmol/L)	L84	-10.22^{Ac}±1.77	-2.18^{Bb}±2.20	5.20^{Aa}±2.20	6.90^{Aa}±3.11
	B84	-10.40^{Ac}±2.32	1.13^{Ab}±4.34	4.98^{Aa}±2.51	3.39^{Ba}±2.59
Na^+ (mmol/L)	L84	156.78^{Aa}±11.32	155.79^{Aab}±11.57	154.02^{Aab}±10.61	153.17^{Ab}±9.26
	B84	154.93^{Aa}±11.58	150.12^{Ab}±10.78	149.27^{Ab}±10.35	151.34^{Ab}±9.41
K^+ (mmol/L)	L84	5.06^{Aa}±1.48	3.48^{Ab}±0.92	3.04^{Ab}±0.61	3.20^{Ab}±0.42
	B84	4.35^{Aa}±1.33	3.48^{Ab}±1.20	3.06^{Ab}±0.83	3.00^{Ab}±0.76
Cl^- (mmol/L)	L84	119.30^{Aa}±7.77	116.88^{Aa}±11.91	109.94^{Aab}±8.43	108.38^{Ab}±8.16
	B84	118.21^{Aa}±8.38	111.41^{Aa}±9.51	107.83^{Ab}±6.57	109.57^{Aab}±7.32
SID_3 (mmol/L)	L84	42.54^{Ab}±5.06	42.39^{Ab}±12.89	47.12^{Aa}±6.02	47.99^{Aa}±3.97
	B84	41.07^{Ab}±6.48	42.19^{Ab}±8.18	44.50^{Aa}±6.88	44.77^{Aa}±4.93
AG (mmol/L)	L84	25.51^{Aa}±5.79	19.28^{Ab}±13.56	16.96^{Ab}±6.87	16.08^{Ab}±4.66
	B84	24.46^{Aa}±7.30	15.71^{Ab}±9.24	14.88^{Ab}±8.44	16.72^{Ab}±6.28
TP (g/dL)	L84	8.54^{Aa}±1.44	7.00^{Ab}±1.61	5.84^{Ac}±1.23	6.48^{Ab}±0.96
	B84	8.20^{Aa}±1.26	6.32^{Ab}±1.27	5.86^{Ac}±0.95	6.41^{Ab}±1.16
A_{tot} (mmol/L)	L84	35.01^{Aa}±5.92	28.70^{Ab}±6.61	23.94^{Ac}±5.03	26.56^{Ab}±3.94
	B84	33.62^{Aa}±5.18	25.91^{Ab}±5.23	24.02^{Ac}±3.90	26.28^{Ab}±4.75
L-lactate (mmol/L)	L84	1.53^{Ac}±0.65	4.26^{Ab}±1.81	5.71^{Aa}±2.24	1.35^{Ac}±0.34
	B84	1.51^{Aa}±0.65	2.07^{Ba}±1.17	1.54^{Ba}±0.64	1.53^{Aa}±0.54
SIG (mmol/L)	L84	-8.57^{Ab}±4.73	-3.52^{Aa}±13.26	-3.11^{Aa}±6.88	-0.55^{Aa}±4.25
	B84	-8.09^{Ab}±5.86	-1.22^{Aa}±7.81	-0.86^{Aa}±7.13	-1.52^{Aa}±4.58
%PV (%)	L84	0^{Ac}	24.48^{Ab}±17.14	49.25^{Aa}±25.56	31.93^{Ab}±12.25
	B84	0^{Ab}	31.39^{Aa}±14.26	40.53^{Aa}±12.27	28.60^{Aa}±8.29

^{A,B,a,b,c,} Means followed by different letters, lowercase in the row and uppercase in the column, differ from each other ($P < 0.05$).

Table 2. Urine values (mean ± SD) of pH and specific gravity, and median values of urine fractional clearances (FC) of Na^+, K^+, Cl^-, and L-lactate in acidotic diarrheal calves before the beginning (0 h), in the middle (2.5 h), at the end (5 h) and 2.5 hours after the end (7.5 h) of the intravenous infusion of polyionic solutions (PS) containing 84 mEq/L of lactate (L84; n = 10) or 84 mEq/L of bicarbonate (B84; n = 10)

Variable	PS	0 h	2.5 h	5 h	7.5 h
pH	L84	5.304^{Ac}±0.37	5.310^{Abc}±0.45	5.685^{Aab}±0.59	6.021^{Aa}±0.67
	B84	5.338^{Ac}±0.25	5.411^{Abc}±0.33	5.503^{Aab}±0.37	5.663^{Aa}±0.57
Specific gravity	L84	1026.2^{Aa}±10.68	1019.0^{Ab}±8.06	1015.4^{Ab}±6.25	1020.0^{Ab}±6.18
	B84	1028.1^{Aa}±5.62	1023.3^{Ab}±7.30	1019.4^{Ab}±8.84	1019.2^{Ab}±6.05
FC Na^+ (%)	L84	0.36^{Ab}	0.86^{Aab}	2.25^{Aa}	0.84^{Aab}
	B84	0.14^{Ab}	0.19^{Ab}	0.96^{Aa}	0.78^{Aab}
FC K^+ (%)	L84	26.299^{Ab}	35.500^{Aab}	52.878^{Aa}	30.081^{Aab}
	B84	16.251^{Ab}	18.889^{Aab}	22.374^{Aa}	20.926^{Aa}
FC Cl^- (%)	L84	2.151^{Ab}	1.627^{Aab}	3.059^{Aa}	1.614^{Aab}
	B84	0.770^{Aa}	0.505^{Aa}	1.039^{Aa}	1.534^{Aa}
FC L-lactate (%)	L84	1.034^{Aab}	0.807^{Ab}	0.869^{Aab}	1.417^{Aa}
	B84	0.893^{Aa}	0.525^{Aa}	0.684^{Aa}	0.443^{Aa}

^{A,B,a,b,c,} Means or medians followed by different letters, lowercase in the row and uppercase in the column, differ from each other ($P < 0.05$).

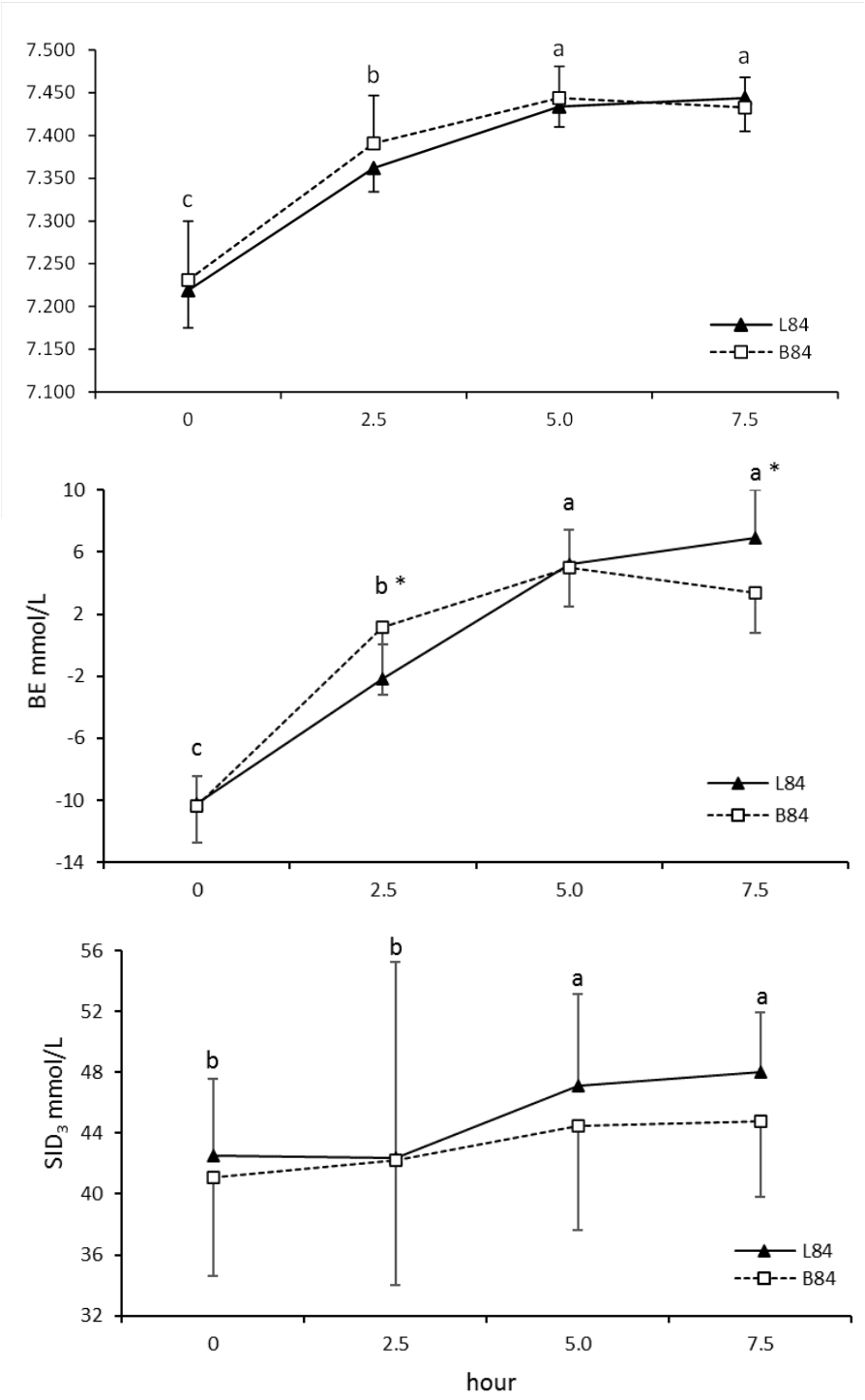

Figure 1. Venous blood pH, BE, and strong ion difference (SID_3) in acidotic diarrheal calves treated with IV infusion of polyionic solutions containing 84 mEq/L of lactate (L84; n = 10) or 84 mEq/L of bicarbonate (B84; n = 10). Values (mean and SD) found before the beginning (0 h), in the middle (2.5 h), at the end (5 h), and 2.5 h after the end (7.5 h) of the IV infusion. Different letters represent difference between moments ($P < 0.05$); * represents difference between treatments ($P < 0.05$).

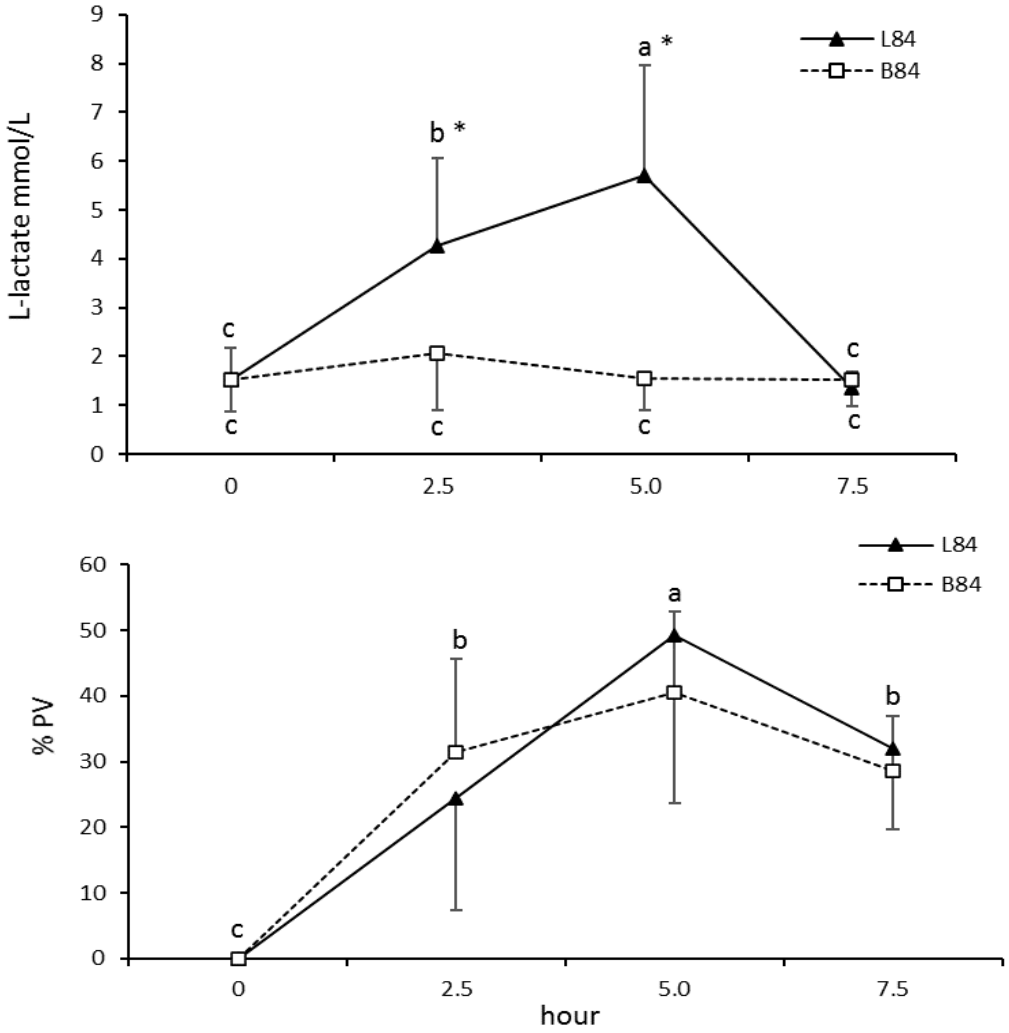

Figure 2. Plasma L-lactate concentration and percentage change in plasma volume (% PV) of acidotic diarrheal calves treated with IV infusion of polyionic solutions containing 84 mEq/L of lactate (L84; n = 10) or 84 mEq/L of bicarbonate (B84; n = 10). Values (mean and SD) found before the beginning (0 h), in the middle (2.5 h), at the end (5 h), and 2.5 h after the end (7.5 h) of the IV infusion. Different letters represent difference between moments ($P < 0.05$).

Plasma concentrations of Na^+, K^+, and Cl^- decreased with the infusion of the L84 solution. The hyperchloremia was effectively reversed at the end of administration and the hypernatremia was almost corrected 2.5 h later. In part, this could be credited to the hemodilution effect, but, certainly, renal correction through selective ion excretion was of paramount importance in this process (DiBartola, 2012). It is logical to admit that blood volume correction promoted an increase in renal blood perfusion and an increase in the glomerular filtration rate, optimizing the mechanisms for correcting electrolyte imbalances. In fact, the FC of Na^+, K^+, and Cl^- increased with the intravenous infusion of L84.

Metabolic acidosis was effectively corrected with the infusion of L84 solution. Acidemia was reversed already in the middle of the intravenous administration period, and the low pH, HCO_3^-, and BE values gradually increased until the end of the infusion, remaining high 2.5 h later. The average increase in the BE value was 15mmol/L, which reinforces the results of previous studies

with healthy (Pereira *et al*., 2021) or acidotic animals (Romão *et al*., 2015; Pereira *et al*. 2022), but differs from other studies with healthy (Junqueira *et al*., 2015; Flaiban *et al*., 2009; Pinto *et al*., 2018) or acidotic (Flaiban, 2010) animals, in which L84 promoted an average increase of 10 mmol/L in BE. This discrepancy can be explained by the difference in the total volume infused. In all previous studies the animals received volume corresponding to 10% BW, whereas in the calves studied the volume corresponded to 12.5% BW.

The alkalizing capacity of the L84 solution is due to its electrolyte composition being different from that of plasma, containing low concentrations of Cl^- and, consequently, high $SID_{3\ effective}$ (84 mmol/L). Unlike LRS, which when infused in healthy animals does not cause iatrogenic electrolyte and acid-base imbalances (Cosenza *et al.*, 2013) precisely because it has an electrolyte composition similar to that of plasma and a $SID_{3\ effective}$ of 28 mmol/L, the L84 solution causes iatrogenic strong ion metabolic alkalosis. This effect has been proven in healthy calves (Junqueira *et al.*, 2015), sheep (Flaiban *et al.*, 2009), horses (Pinto *et al.*, 2018), and goats (Pereira *et al.*, 2021) and is due to the reduction in chloremia with consequent increase in plasma SID_3. The studied diarrheal calves showed exactly these same plasma variations, and this promoted the correction of the metabolic acidosis. According to the strong ion theory, electrolyte solutions with high $SID_{3\ effective}$ (> 40 mmol/L) are therefore alkalizing, whereas those with reduced $SID_{3\ effective}$ (close to 0 mmol/L) have acidifying capacity (Constable, 2014; Constable *et al*., 2021).

In experimental studies, the L84 solution was efficient to correct hyperchloremic metabolic acidosis in horses (Romão *et al.*, 2015) and metabolic acidosis due to the accumulation of organic acids in sheep (Flaiban, 2010) and goats (Pereira *et al.*, 2022) with ARLA. In the present study, this solution was proven effective for correcting metabolic acidosis likely due to hyper-D-lactatemia. The increase in SIG values to close to 0 mmol/L is proof that the accumulation of unmeasured organic acids, especially D-lactate, has been reversed. Because it is poorly metabolized, D-lactate is eliminated from the body through the urine (Lorenz and Gentile, 2014) and, certainly, the expansion of plasma volume by itself contributed to this process by improving renal blood flow and the rate of glomerular filtration in the studied calves. However, this mechanism is not the only one involved, as the increase in blood volume with LRS infusion was not accompanied by the reversal of metabolic acidosis in sheep affected by ARLA (Cosenza *et al.*, 2015). The alkalizing properties of the L84 solution must, therefore, have played a fundamental role.

The effects caused by the infusion of the L84 solution did not differ from those caused by the administration of the B84 solution, except for the hyper-L-lactatemia resulting from the administration of the L84. The B84 solution was used in this study as a standard for comparison with L84, since the buffering effect of the bicarbonate ion is immediate, originating CO_2 and water. In the case of L84, there is a need to metabolize lactate ions for the alkalizing effect to be achieved, as the permanence of lactate ions recently infused in the plasma would delay alkalinization because there would be no increase in plasma SID (Constable *et al.*, 2021). Therefore, the alkalizing effect of the B84 solution would theoretically be faster. This has not been confirmed exactly because L-lactate was metabolized very quickly. The iatrogenic hyper-L-lactatemia was reversed 2.5 h after the end of the infusion and the FC of lactate did not increase, which indicates that L-lactate was not excreted in the urine. These results reinforce previous observations in healthy calves (Junqueira *et al.*, 2015), proving that the metabolism of infused L-lactate is fast even in dehydrated and acidotic diarrheal calves, probably with hyper-D-lactatemia. The absence of differences between the effects of the two solutions also reinforces previous results in acidotic ewes (Flaiban, 2010) and goats (Pereira *et al.*, 2022).

CONCLUSION

It can be concluded that the polyionic intravenous solution containing a high concentration of lactate (84mEq/L) is effective for the treatment of calves with induced diarrhea, reversing dehydration, hyperchloremia and metabolic acidosis due to the accumulation of organic acids. Its effectiveness for the treatment of calves suffering from naturally occurring diarrhea must be proven in clinical practice.

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