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Intravenous Hypertonic Saline Solution (7.5%) and Oral Electrolytes to Treat of Calves with Noninfectious Diarrhea and Metabolic Acidosis

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Objective: The aim of this study was to compare the efficacy of treating osmotic diarrhea and dehydration in calves with hypertonic saline solution (HSS) IV, isotonic electrolyte solution (IES) PO, and a combination of these 2 solutions (HSS + IES).

Experimental Design: Eighteen male calves 8–30 days of age were used to evaluate the efficacy of 3 methods of fluid therapy after induction of osmotic diarrhea and dehydration. The diarrhea and dehydration were induced by administration of saccharose, spironolactone, and hydrochlorothiazide for 48 hours. The animals were randomly divided into 3 experimental groups: Group 1: 7.2% hypertonic saline solution-HSS (5 mL/kg IV); Group 2: oral isotonic electrolyte solution IES (60 mL/kg PO); or Group 3: HSS+IES. Clinical signs and laboratory finding observed 48 hours post-induction (Time 0) included diarrhea, dehydration, lethargy, and metabolic acidosis.

Results: Calves treated with HSS + IES experienced decreases in hematocrit, total protein concentration, albumin concentration, urea nitrogen concentration, and plasma volume as well as increases in blood pH, blood bicarbonate concentration, and central venous pressure between 1 and 3 hours post-treatment. These findings also were observed in animals treated with IES, however, at a slower rate than in the HSS + IES-treated animals. Animals treated with HSS continued to display signs of dehydration, lethargy, and metabolic acidosis 24 hours post-treatment.

Conclusion: Treatment with a combination of HSS and IES produced rapid and sustainable correction of hypovolemia and metabolic acidosis in calves with noninfections diarrhea and dehydration.

Key words: Calves; Dehydration; Diarrhea; Induction; Treatment.

Neonatal diarrhea is a major problem in the livestock industry.[1,2] This form of diarrhea can lead to death of calves because of water electrolyte and acid base imbalances.[3] Correcting these imbalances is critical to minimize the mortality rate of diarrhea syndrome in calves. Correcting dehydration, water, electrolyte, and acid base imbalances PO is preferable, because it represents a low-cost alternative and provides an easy method of treatment.[4] The oral route is contraindicated in cases of paralytic ileus, when animals show acute fluid loss.[5]

Intravenous (IV) treatment is necessary to rapidly replace fluids and electrolytes.[4,5] Traditionally, isotonic crystalloid solutions, including 0.9% sodium chloride, 5% glucose, and simple Ringer's or lactated Ringer's solution, have been utilized for IV hydration. However, there are many difficulties involved in using crystalloid solutions. Specifically, large volumes of fluids are required, a large amount of time is spent on administration of the fluids, and venous catheterization and frequent monitoring are required with this method of treatment.[6]

Abbreviations:

BE	base excess
CVP	central venous pressure
HCO^-_3	blood concentration of actual bicarbonate
HSS	hypertonic saline solution
IES	oral isotonic electrolyte solution
IV	intravenous
pCO_2	carbon dioxide pressure
pH	blood pH
PI	post-induction
PO	oral
pO_2	oxygen pressure
PT	post-treatment
PVD	plasma volume deficit
SIG	strong ion gap

To address these difficulties, a number of studies have examined alternative methods for IV replacement of fluids. Small quantities of HSS (7.2%) were shown to be an efficient treatment in animals with hypovolemic shock, severe dehydration,[7,8] and endotoxemia.[9] This type of treatment should be supplemented with another solution, because the positive effect produced by treatment with HSS is brief (approximately 2 hours) and because this treatment results in considerable increases in serum concentrations of sodium and chloride.[10] In addition, HSS does not correct acid base imbalance and exacerbates metabolic acidosis.[4] Absorption of PO administered fluid can be facilitated by IV administration of hypertonic saline-dextran (HDS) solution.[10] This solution can induce a rapid increase in plasma volume and cardiac output in calves by shifting fluid from the intracellular space and gastrointestinal tract.[5] Previous studies evaluated the use

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of HDS together with an oral alkalinizing solution in calves with diarrhea.[10,11] None of these experiments led to metabolic acidosis, an important cause of lethargy and death in calves with diarrhea and dehydration. Based on these results, the aim of this study was to compare the combination of HSS (IV-7.2%) without dextran and IES with administration of either solution alone in calves with watery diarrhea, severe dehydration, and acidosis, induced by saccharose and diuretics.

Materials and Methods

Calves

Eighteen healthy Holstein calves, between 8 and 30 days of age with body weight ranging from 37 to 50 kg, were used. The calves were housed individually in galvanized cages installed in stalls located at the Clinic for Ruminants of the School of Veterinary Medicine and Animal Science at the Universidade de São Paulo. Calves were fed whole milk at the rate of 10% of their body weight per day divided into 2 feedings at 8:00 and 17:00. Water was available ad libitum. Before the start of the experiment, the calves were kept in their stalls for a minimum of 5 days to adapt to the diet and their surroundings. The animals selected for the study were considered healthy after physical examination as well as electrocardiographic[b] and echocardiographic[c] examinations.

Instrumentation

On the day before the experiment, IV catheters [d]were implanted in the animals to measure central venous pressure (CVP) and collect blood samples. The needle was withdrawn after introducing the catheter into the right atrium and needle was retracted into a shielding device, which was secured to the skin with 1.0 nylon suture. The catheter was flushed with 10 mL 0.9% NaCl solution containing sodium heparin (50 IU/mL)[e] every 8 hours to prevent coagulation in the catheter.

Induction of Diarrhea and Dehydration

Osmotic diarrhea and dehydration were induced by administration of whole milk (16.5 mL/kg),[f] saccharose (4 g/kg as a 20% aqueous solution), spirolactone (2 mg/kg),[g] and hydrochlorothiazide (2 mg/kg)[h] PO every 8 hours for a period of 48 hours.[11] The spironolactone and hydrochlorothiazide tablets were crushed and diluted in 10 mL of distilled water and given PO in 20-mL syringes.

Experimental Protocol

The fecal score (determining the level of consistency of the feces), degree of dehydration, and extent of lethargy were judged using the indices reported by Walker et al.[12] Evaluations were performed by a person who was previously trained. This evaluator was unaware of the group to which each animal belonged. The fecal scores utilized were 0 = normal, wellformed feces (firm); 1 = abnormal with a tendency for the feces to be pasty but not diarrheic; 2 = pasty feces with moderate diarrhea; 3 = watery feces with severe diarrhea. The degrees of clinical dehydration were 0 = normal with bright eyes and normal skin turgor; 1 = mild with slightly decreased skin turgor as well as sticky oral mucosa, congested episcleral vessels, and loss of body weight between 6 and 8%; 2 = moderate with slightly retracted ocular globes, an evident decrease in skin turgor, dry oral mucosa, and a loss of body weight between 8 and 10%; 3 = severe with wellretracted ocular globes, marked decrease in skin turgor, cold nose, cold oral cavity, and > 10% loss of body weight. The degrees of lethargy were 0 = normal; 1 = mild, with the calf nursing but not vigorously nursing; 2 = moderate, with the calf remained on station but slow or disorganized suckling; 3 = severe, with the calf demonstrating inability to nurse or remain in the station.

The animals were monitored at Time 0 (48 hours after induction of diarrhea and dehydration -PI) 1, 3, 6, 12, 24, 48 and 72 hours post-treatment (PT). Body weight was determined at 24, 48, and 72 hours PT. Blood was collect in tubes containing sodium fluoride, and plasma was harvested in tubes without anticoagulants. To determine the packed cell volume, blood samples were collected with EDTA (ethylenediamine tetraacetic acid). After collection, blood samples were centrifuged for 30 minutes. Plasma and serum were stored for up to 2 months at −70°C.

Samples for blood gas analysis were collected directly from the catheter using 2 mL syringes containing 100 IU of sodium heparin. To avoid contact of blood with the environment, routine care was taken during and after collection, consisting of slow suction, removing any gas bubble in the sample and sealing of the needle tip with rubber stopper before sample mixing.

The packed cell volume was determined using a microhematocrit centrifuge.[i] Total protein, albumin, urea, and creatinine were determined on serum. Glucose and L-lactate were determined using plasma. These biochemical components were quantified using an automatic biochemical analyzer.[j] Blood gas variables were quantified with an automatic analyzer for pH and blood gases[k] (pH, HCO^-_3, BE, pO_2, pCO_2). Serum sodium, chloride, and potassium concentrations were determined using an automated analyzer and ion selective electrodes.[k] Plasma volume deficit (PVD) was calculated using a mathematical expression that relates the hematocrit at time zero (Ht^I) to the hematocrit obtained at subsequent time points (Ht_N)[13]:

$$\text{Plasma volume deficit \%} = \left\{ \left(\frac{Ht_1(1 - Ht_N)}{Ht_N(1 - Ht_1)} - 1 \right) \times 100 \right\}$$

The anion gap was determined as (serum sodium concentration + serum potassium concentration) − (serum chloride concentration + blood bicarbonate concentration).[13,14] The strong ion gap (SIG) was determined as [albumin] × $(0.622/\{1 + 10^{[7.08-pH]}\})$ − anion gap. The CVP was determined within the right atrium; the scapulohumeral joint served as the zero point. Measurements were taken with the calf standing with its head in a typical alert, nonfeeding, forward-facing position. Change in height of the column was measured in cm of H_2O.[11,12,15] All of the animals were tested by B-mode echocardiogram[k] to confirm the position of the catheter within the right atrium. The animals were distributed randomly into 3 experimental groups of 6 calves each and received the after treatments: the HSS group was treated with hypertonic saline solution (7.2% NaCl or 2.400 mOsm/L) beginning at Time 0 IV at a rate of 5 mL/kg over a period of 3–10 minutes. The IES group was treated with isotonic electrolyte solution at a concentration of 300 mOsm/L (Table 1) at a rate of 60 mL/kg (Time 0). IES solution was repeated twice at 8 and 16 hours after initial treatment. The IES was administered to calves in baby bottles. The IES + HSS group received the same treatment as the HSS group followed by the treatment given to the IES group.

Fresh water was provided ad libitum after administration of the solutions (PO and IV), and 24 hours after the treatment period the calves were fed the diet they received before the beginning of the experiments. Administration of spironolactone and

Table 1. Composition of the oral isotonic electrolyte solution per liter of water.

Constituents	Quantity (g)
Sodium chloride (NaCl)	3.22
Potassium chloride (KCl)	1.12
Sodium acetate trihydrate ($NaC_2H_3O_2.3H_2O$)	4.76
D–Glucose, anhydrous ($C_6H_{12}O_6$)	16.22

Na: 90 mmol/L; Cl: 70 mmol/L; K: 15 mmol/L; acetate: 35 mmol/L; glucose: 90 mmol/L (from Constable et al[10]).

hydrochlorothiazide were discontinued at the time, but the milk replacer and isotonic saccharose in 19.5 mL of water/kg were continued until the end of the treatment (24 hours).

Commission on Bioethics

This work was carried out according to the principles of the Commission on Bioethics of the School of Veterinary Medicine and Animal Science at the University of São Paulo (Number 1198/2007).

Statistical Analysis

Two-way ANOVA (time, treatment with repeated measures on factor time)[m] was used for comparison of continuous variables. Multiple pair-wise comparisons were conducted between or within groups, using post-hoc Duncan's test to compare means. Between groups comparisons for each variable were made at each time point after induction of diarrhea. The ordinal variables (fecal score, degree of dehydration, and degree of lethargy) and nonnormally variables (CVP, PVD, and SIG) were subjected to the method Npar1way nonparametric analysis of variance and the Kruskal–Wallis's test. P values < .05 were considered significant. The Pearson correlation coefficient was calculated between the measurement means and the differences between each pair of measurements to test whether the data had heteroscedastic error. Data from ordinal variables are presented as medians; other data are presented as means and standard deviations.

Results

Induced diarrhea and dehydration using saccharose and 2 types of diuretics resulted in profuse diarrhea, severe hypovolemia as well as alterations in acid base balance (metabolic acidosis). All of the calves maintained their ability to suckle and shower during the induction period, even though they appeared weak and showed signs of moderate lethargy. Mean weight loss was 5.1 kg per animal, which corresponded to approximately 13% of the average body weight.

The diarrhea and dehydration did not result in mortality. Hypovolemia and decreased glomerular filtration rate were reflected by a significant increase in hematocrit, total protein concentration, albumin concentration, urea concentration, creatinine concentration, PVD, maximum degree of clinical dehydration, and decrease in CVP. Metabolic acidosis was confirmed by the decrease in pH, HCO^-_3, BE, and SIG, as well as by increase of anion gap.

Forty-eight hours after induction of diarrhea and dehydration, the calves in all groups showed the maximum degree of clinical dehydration (Table 3). A gradual reduction was observed in the degree of clinical dehydration 24 hours PT in the IES and HSS + IES groups (Fig 2). In the HSS group, the animals continued to exhibit moderate degree of dehydration up to 24 hours PT (Fig 2). The PVD in the IES-treated animals gradually decreased at 24 hours PT (Fig 2). The HSS treated group had higher PVD 24 hours PT. The calves from the group treated with HSS + IES, however, had plasma volume in the 1 hour after treatment, demonstrating that the combined treatment caused a rapid and constant rebound of plasma volume (Fig 2).

Central venous pressure in the HSS group increased 1 hour after treatment, but this increase was transient (Fig 3). The animals in this group only showed higher values of CVP 24 hours PT. The calves in the IES group showed a slower recovery of CVP compared with the HSS + IES group. The CVP values in the group treated with HSS + IES remained constant until the end of the study (Fig 3). There was a moderate negative correlation between PVD and CPV ($r = -0.67$, $P < .001$).

After induction of diarrhea and dehydration (0 hours), L-lactate concentration was higher in the IES group. Before induction of diarrhea, however, the animals in this group had more biochemical abnormalities than the other groups. Higher concentrations of L-lactate were observed in all groups at Time 0 and 1 hour PT compared with other experimental times.

Creatinine and urea concentrations increased well above normal in all experimental groups (0 hours). Administration of IES and HSS + IES caused a gradual decrease in serum urea concentrations during the treatment phase (Table 2). Animals treated with HSS had high concentration of urea up to 24 hours PT (Table 2). Because the serum creatinine concentrations did not differ significantly from normal, the solutions utilized in this study (HSS, IES and HSS + IES) are likely capable of decreasing creatinine concentrations between 6 and 12 hours PT.

No differences were observed in serum sodium and chloride concentrations at 0 hours (Table 2). Sodium concentrations increased 1 hour after treatment in animals receiving HSS or HSS + IES. Serum chloride concentrations decreased from 6 to 12 hours PT, respectively, in the groups treated with hypertonic saline (HSS or HSS + IES). No differences were observed in the concentrations of these ions in the IES group (Table 2). Serum potassium concentrations increased in the 3 experimental groups at 0 hours (Table 2). Treatment with HSS, IES, and HSS + IES (Table 2) rapidly reversed hyperkalemia in the 1st hour after treatment. However, the animals treated with HSS alone showed lower potassium concentrations at 24 hours PT.

Plasma glucose concentrations (Table 2) did not differ after induction of diarrhea in the experimental groups. After induction of diarrhea, plasma glucose concentrations gradually decreased until 24 hours PT in the animals that received HSS. In the animals

Table 2. Results of laboratory analyses and physical examination from severely dehydrated calves with diarrhea.

Variables	0 hours	1 hour PT	3 hours PT	6 hours PT	12 hours PT	24 hours PT	48 hours PT	72 hours PT
Hematocrit (%)								
HSS	$37.6 \pm 3.5^{A*a}$	32.7 ± 3.9^{Ab}	31.3 ± 3.5^{ABc}	31.7 ± 3.5^{Ac}	32.3 ± 3.8^{Abc}	32.7 ± 3.0^{Abc}	31.2 ± 3.3^{Ac}	31.0 ± 3.3^{Ac}
IES	36.2 ± 4.6^{Aa}	32.0 ± 3.9^{Ab}	32.0 ± 4.3^{Ab}	32.2 ± 4.0^{Ab}	30.8 ± 3.5^{ABc}	30.2 ± 5.0^{Bc}	30.2 ± 4.4^{Ac}	29.8 ± 4.2^{Ac}
HSS +IES	34.6 ± 5.0^{Aa}	28.0 ± 3.8^{Ab}	27.2 ± 3.2^{Bb}	29.0 ± 5.6^{Aab}	28.4 ± 5.0^{Bb}	27.4 ± 4.2^{Bb}	27.0 ± 3.3^{Ab}	27.4 ± 4.9^{Ab}
Total Protein (g/dL)								
HSS	7.20 ± 0.9^{Aa}	6.52 ± 0.6^{Aab}	6.34 ± 0.7^{Ab}	6.40 ± 0.6^{Ab}	6.43 ± 0.8^{Ab}	6.41 ± 0.9^{Ab}	6.27 ± 0.6^{Ab}	6.14 ± 0.7^{Ab}
IES	$7.43 \pm 0.^{9Aa}$	6.61 ± 0.9^{Aab}	6.41 ± 0.8^{Aab}	6.24 ± 0.9^{Aab}	6.07 ± 0.9^{ABb}	6.00 ± 0.9^{ABb}	6.15 ± 0.9^{Aab}	6.39 ± 0.8^{Aab}
HSS +IES	6.71 ± 0.8^{Aa}	5.80 ± 0.6^{Ab}	5.82 ± 0.6^{Ab}	5.84 ± 0.7^{Ab}	5.63 ± 0.6^{Bb}	5.60 ± 0.6^{Bb}	5.80 ± 0.6^{Ab}	5.71 ± 0.7^{Ab}
Urea (mg/dL)								
HSS	73.1 ± 9^{Aa}	66.5 ± 10^{Aa}	55.9 ± 10^{Aab}	50.5 ± 9^{Ab}	45.7 ± 12^{Ab}	41.2 ± 11^{Ab}	31.2 ± 9^{Ac}	20.1 ± 5^{Ac}
IES	61.2 ± 10^{Aa}	56.2 ± 9^{Aa}	47.9 ± 8^{Aab}	38.3 ± 10^{Ab}	30.6 ± 6^{Bb}	18.7 ± 10^{Bc}	18.6 ± 5^{Bc}	21.6 ± 5^{Ac}
HSS +IES	71.4 ± 17^{Aa}	67.2 ± 18^{Aa}	56.4 ± 15^{Aab}	50.6 ± 13^{Ab}	36.4 ± 10^{Bb}	24.4 ± 17^{Bc}	21.6 ± 3^{Bc}	22.5 ± 17^{Ac}
Creatinine (mg/dL)								
HSS	2.2 ± 0.3^{Aa}	1.9 ± 0.4^{Aa}	1.7 ± 0.2^{Aa}	1.6 ± 0.2^{Aab}	1.6 ± 0.2^{Aab}	1.6 ± 0.2^{Ab}	1.3 ± 0.2^{Ab}	1.3 ± 0.2^{Aab}
IES	2.5 ± 0.4^{Aa}	2.3 ± 0.4^{Aa}	2.0 ± 0.2^{Aa}	1.8 ± 0.3^{Aab}	1.7 ± 0.2^{Aab}	1.5 ± 0.3^{Ab}	1.5 ± 0.3^{Ab}	1.5 ± 0.3^{Aab}
HSS +IES	2.4 ± 0.5^{Aa}	2.2 ± 0.4^{Aa}	2.0 ± 0.2^{Aa}	1.8 ± 0.3^{Aab}	1.6 ± 0.2^{Aab}	1.5 ± 0.3^{Ab}	1.5 ± 0.3^{2b}	1.4 ± 0.3^{Aab}
L-lactate (mmol/L)								
HSS	1.8 ± 0.7^{ba}	1.6 ± 0.5^{Ba}	1.1 ± 0.3^{Bb}	1.1 ± 0.2^{Bb}	0.8 ± 0.2^{Bc}	0.9 ± 0.3^{Abc}	0.9 ± 0.3^{Abc}	0.9 ± 0.3^{Abc}
IES	2.0 ± 0.6^{Ab}	2.7 ± 0.8^{ABa}	2.1 ± 0.1^{ABb}	1.8 ± 0.6^{ABb}	1.8 ± 0.9^{ABb}	1.1 ± 0.3^{Ac}	1.2 ± 0.3^{Ac}	1.2 ± 0.3^{Ac}
HSS +IES	3.0 ± 1.4^{Aa}	3.4 ± 2.5^{Aa}	2.2 ± 0.8^{Ab}	2.1 ± 1.4^{Ab}	2.1 ± 1.2^{Ab}	2.0 ± 1.3^{Ab}	1.6 ± 0.8^{Ac}	1.7 ± 0.7^{Ac}
Degree of dehydration*								
HSS	3.0^{Aa}	3.0^{Aa}	2.0^{Ab}	2.0^{Ab}	2.0^{Ab}	1.0^{Ac}	0.0^{Ad}	$0.0\pm^{Ad}$
IES	3.0^{Aa}	2.0^{Ab}	2.0^{Ab}	1.5^{Ab}	1.0^{ABc}	0.0^{Bd}	0.0^{Ad}	0.0^{Ad}
HSS +IES	3.0^{Aa}	2.2^{Aab}	2.0^{Ab}	1.2^{Ac}	1.0^{Bc}	0.2^{Bcd}	0.0^{Ad}	0.0^{Ad}
Sodium (mmol/L)								
HSS	141.2 ± 10^{Ab}	146.3 ± 12^{Aa}	138.2 ± 11^{Ab}	136.1 ± 10^{Ab}	135.1 ± 11^{Ab}	133.9 ± 10^{Ab}	136.4 ± 8^{Ab}	137.6 ± 11^{Ab}
IES	142.4 ± 12^{Aa}	143.1 ± 13^{Aa}	140.4 ± 12^{Aa}	137.8 ± 11^{Aa}	137.2 ± 10^{Aa}	138.8 ± 10^{Aa}	139.6 ± 8^{Aa}	140.8 ± 12^{Aa}
HSS +IES	137.1 ± 6^{Ab}	142.9 ± 9^{Aa}	135.1 ± 8^{Ab}	130.4 ± 5^{Ab}	132.2 ± 6^{Ab}	136.4 ± 3^{Aab}	129.8 ± 5^{Ab}	131.4 ± 4^{Ab}
Chloride (mmol/L)								
HSS	108.3 ± 8^{Aab}	114.0 ± 9^{Aa}	107.8 ± 8^{Aab}	105.1 ± 7^{Aab}	103.7 ± 7^{Ab}	101.3 ± 6^{Ab}	102.9 ± 6^{Ab}	105.2 ± 6^{Aab}
IES	111.5 ± 13^{Aa}	108.9 ± 11^{Aa}	106.6 ± 10^{Aa}	105.7 ± 8^{Aa}	104.1 ± 7^{Aa}	104.2 ± 8^{Aa}	103.4 ± 6^{Aa}	103.9 ± 5^{Aa}
HSS +IES	107.2 ± 5^{Aabc}	112.8 ± 6^{Aa}	108.2 ± 5^{Aab}	104.6 ± 2^{Ab}	104.4 ± 4^{Ab}	101.9 ± 3^{Ac}	100.3 ± 3^{Ac}	100.3 ± 3^{Ac}
Potassium (mmol/L)								
HSS	5.5 ± 0.5^{Aa}	4.9 ± 0.6^{Aab}	4.4 ± 0.5^{Ab}	4.3 ± 0.5^{Ab}	4.0 ± 0.5^{Ac}	3.9 ± 0.4^{Ac}	4.6 ± 0.4^{Ab}	4.7 ± 0.4^{Ab}
IES	5.6 ± 0.7^{Aa}	4.9 ± 0.6^{Aab}	4.9 ± 0.5^{Ab}	4.8 ± 0.6^{Ab}	4.5 ± 0.4^{Ac}	4.5 ± 0.9^{Ac}	4.6 ± 0.6^{Ab}	4.6 ± 0.6^{Ab}
HSS +IES	5.7 ± 1.1^{Aa}	5.2 ± 1.0^{Aab}	4.6 ± 0.9^{Ab}	4.5 ± 0.4^{Ab}	4.2 ± 0.7^{Ac}	4.2 ± 0.4^{Ac}	4.2 ± 0.4^{Ac}	4.2 ± 0.2^{Ac}
Glucose (mg/dL)								
HSS	95.8 ± 16^{Aa}	89.3 ± 7^{Cb}	72.5 ± 16^{Ac}	78.2 ± 13^{Ab}	70.5 ± 15^{Bc}	59.2 ± 14^{Cd}	80.5 ± 24^{Ab}	78.8 ± 14^{Ab}
IES	102.3 ± 12^{Ab}	154.3 ± 23^{Aa}	79.5 ± 12^{Ab}	80.5 ± 17^{Ab}	83.2 ± 24^{Ab}	75.3 ± 19^{Bb}	76.0 ± 22^{Ab}	74.7 ± 22^{Ab}
HSS +IES	102.2 ± 10^{Ab}	127.2 ± 20^{Ba}	83.0 ± 25^{Ab}	83.0 ± 25^{Ab}	91.8 ± 15^{Aab}	91.8 ± 15^{Aab}	84.0 ± 10^{Aab}	91.6 ± 19^{Aab}

*Values are reported as median.

^{A,B}Significantly between groups ($P < .05$). ^{a,b,c}difference Significantly between experimental times ($P < .05$).

HSS (treatment with hypertonic saline solution); IES (treatment whit isotonic electrolyte solution); HSS+IES (treatment with hypertonic saline solution and oral electrolyte solution.

0 hours = 48 hours after induction of diarrhea and dehydration.

PT = hours after treatment.

Values are reported as mean ± SD.

treated with IES and HSS + IES, an increase was detected in glucose concentrations 1 hour PT. Afterward, glucose concentrations decreased in these 2 groups. In the calves treated with HSS + IES, this reduction was small and glucose concentrations measured in this group were significantly greater than concentrations observed in the other 2 groups at 24 hours PT (Table 2).

Metabolic acidosis was observed at Time 0, characterized by low blood pH and decreased HCO^-_3, BE and SIG, and increased anion gap (Table 3 and Fig 1). There was a high correlation between pH and HCO_3 ($r = 0.74$, $P < .002$) and BE ($r = 0.81$, $P < .001$). The IES and HSS + IES groups had increased values of the previously mentioned variables (pH, hCO_3, BE, and SIG) by 1–12 hours PT (Table 3 and Fig 1). The animals treated with HSS continued to have metabolic acidosis 24 hours PT (Table 3 and Fig 1).There was no significant change pCO_2 after induction of diarrhea and dehydration (Table 3). After treatment, pCO_2 decreased from 3 to 24 hours PT in the HSS group and from 6 to 12 hours PT in the IES and HSS + IES groups.

After induction of diarrhea and dehydration, animals in all experimental groups developed a moderate degree of lethargy (Table 3). The degree of lethargy in animals with diarrhea was related to the severity of metabolic acidosis. During treatment, we observed that the IES and HSS + IES groups (Table 3) recovered more rapidly compared with the HSS group, which exhibited slight lethargy and metabolic acidosis at 24 hours PT (Table 3). Significant body weight loss was observed in all of the animals after the induction of diarrhea and dehydration (Table 3). All calves showed the highest degree of fecal score (0 hours) (Table 3). Normal fecal consistency was observed 48 and 72 hours PT in animals treated with IES and HSS or HSS + IES, respectively.

Discussion

The results indicate that administration of hypertonic saline (without dextran) IV with electrolyte solution (HSS + IES) PO led to rapid and substantial rehydration of calves with severe dehydration (13%) and metabolic acidosis induced by saccharose and diuretics (Tables 2 and 3). The combined treatment increased CVP, pH, HCO^-_3, BE, SIG, and decreased anion gap, hematocrit, serum protein concentration, albumin concentration, urea concentration, creatinine concentration, PVD, and degree of clinical dehydration. HSS + IES together was superior to administration of either solution alone. Isotonic electrolyte solution was more slowly effective in correcting electrolyte and metabolic disorders. The use of HSS was not able to correct dehydration and metabolic acidosis during the treatment phase.

The beneficial effect of the combination HSS (7.2%) with 6% dextran 70 (HSD) and isotonic electrolyte solution has been documented in calves with moderate dehydration (8%).[11] In another study, treatment with HDS and oral electrolyte solution (IES) was compared to administration of a lactated Ringer's IV combined with IES in calves with diarrhea.[10] They observed that the former treatment (HSD + IES) was more rapid and effective for correcting the PVD in calves with severe dehydration.[10] Hypertonic saline solution exerts its resuscitating effect primarily by expanding plasma volume at the expense of translocation of fluid from the intracellular and gastrointestinal spaces to the intravascular space.[4,16,17] The combined use of HSS with an electrolyte solution is necessary to promote movement of water from the gastrointestinal tract to the extracellular space and to replace lost electrolytes.[8,10]. The addition of dextran to HSS prolonged the effects of this solution.[10] This study showed that a combination of HSS + IES, without the addition of dextran, was able to correct severe dehydration in these calves (Tables 2 and 3). The disadvantage of using dextran, besides increasing the cost of treatment per calf, is that dextran can cause coagulopathy as well as an anaphylactic reaction.[18] Hyponatremia, hypochloremia, and hyperkalemia are common in calves with spontaneous diarrhea.[5] Hypernatremia also is observed in calves with diarrhea, and is related to low plasma protein concentrations.[5] In this study, fluid loss was isosmotic because chloride and sodium concentrations were unchanged after induction of diarrhea. However, Sen et al[2] did not observe alterations in serum sodium or chloride concentrations when they evaluated calves with diarrhea caused by unknown factors. In calves with endotoxemia, the use of HSS causes increases in serum sodium and chloride concentrations, but this effect only lasts 60 minutes.[9] According to Kaneko et al,[13] most domestic animals tolerate greater sodium intake if they have adequate access to water. Animals treated with HSS ingested a larger amount of water after treatment compared with other groups, although it was not possible to quantify the amount. Hyperkalemia was observed in all animals after induction of diarrhea (Table 3). Similar results were observed by other authors who used saccharose and 3 types of diuretics to induce diarrhea and dehydration in calves.[10] However, when only saccharose and furosemide were used to induce diarrhea and dehydration, there was no change in serum potassium concentrations.[11] Hyperkalemia occurs by translocation of potassium from the intracellular to the extracellular space in response to low concentrations of sodium in the extracellular fluid, or as a compensatory mechanism for acidosis.[4,13,14] This imbalance responds to rehydration by restoration tissue perfusion, decreasing extracellular potassium concentration, and correcting metabolic acidosis.[4,13] For rehydration to be effective, sodium concentration must be reestablished and Na, K-ATPase can function at full capacity and carry potassium into cells.[13,17] All solutions were able to reduce hyperkalemia. The low potassium concentrations in animals treated with HSS are related to rapid expansion of the extravascular volume and a strong ion effect resulting in extracellular potassium exchange for sodium.[4] Decreased potassium concentration after administration of HSS + dextran has been documented

Table 3. Results of laboratory analyses and physical examination from severely dehydrated calves with diarrhea.

Variables	0 hours	1 hour PT	3 hours PT	6 hours PT	12 hours PT	24 hours PT	48 hours PT	72 hours PT
HCO_3^- (mmol/L)								
HSS	22.5 ± 2.1^{Bb}	20.1 ± 2.2^{Bc}	20.0 ± 2.2^{Bc}	20.0 ± 1.9^{Bc}	20.8 ± 2.5^{Bc}	22.4 ± 3.5^{Bb}	26.6 ± 2.6^{Aa}	27.8 ± 2.3^{Aa}
IES	21.7 ± 2.2^{Bc}	22.9 ± 3.1^{Bb}	22.8 ± 3.1^{Ab}	22.8 ± 2.5^{Ab}	24.6 ± 2.2^{Ab}	28.4 ± 2.0^{Aa}	30.1 ± 1.9^{Aa}	31.0 ± 1.6^{Aa}
HSS +IES	20.8 ± 1.9^{Bc}	21.1 ± 2.8^{Bc}	21.1 ± 2.8^{Ac}	21.7 ± 2.1^{Bb}	24.0 ± 2.2^{ABb}	25.3 ± 2.8^{ABab}	28.8 ± 1.8^{Aa}	27.8 ± 4.2^{Aa}
BE (mmol/L)								
HSS	4.4 ± 1.7^{Bc}	6.5 ± 2.3^{Bc}	6.0 ± 2.2^{Bc}	5.8 ± 2.2^{Bc}	5.0 ± 2.6^{Bc}	-4.1 ± 3.0^{Bc}	1.0 ± 2.3^{Ab}	2.0 ± 1.9^{Aa}
IES	5.1 ± 2.5^{Bc}	3.5 ± 2.2^{Bc}	3.2 ± 2.9^{Ac}	2.0 ± 1.8^{Ac}	1.2 ± 2.6^{Ab}	2.5 ± 1.0^{Aab}	3.9 ± 1.6^{Aa}	4.5 ± 2.0^{Aa}
HSS +IES	6.9 ± 3.5^{Bc}	6.2 ± 3.5^{Bc}	4.8 ± 2.9^{ABc}	3.9 ± 2.0^{ABc}	2.4 ± 2.1^{Ab}	0.6 ± 2.6^{Aab}	2.2 ± 3.3^{Aa}	1.9 ± 2.0^{Aa}
pCO_2 (mmHg)–								
HSS	48.8 ± 4.6^{Aa}	46.6 ± 3.0^{Aa}	41.3 ± 3.7^{Bb}	41.4 ± 2.0^{Ab}	41.4 ± 2.5^{Bb}	44.3 ± 5.8^{Ab}	48.6 ± 3.7^{Aa}	51.6 ± 2.7^{Aa}
IES	48.6 ± 4.9^{Aa}	48.4 ± 4.1^{Aa}	45.5 ± 4.2^{Ab}	45.2 ± 3.7^{Ab}	44.8 ± 2.9^{Ab}	48.6 ± 3.5^{Aa}	51.2 ± 3.7^{Aa}	53.1 ± 3.0^{Aa}
HSS +IES	50.1 ± 6.0^{Aa}	45.5 ± 4.2^{Ab}	43.6 ± 3.3^{ABb}	41.8 ± 3.9^{Ac}	43.0 ± 1.9^{Ab}	45.9 ± 3.4^{Ab}	47.7 ± 4.5^{Aab}	48.0 ± 3.3^{Aa}
Anion gap (mEq/L)								
HSS	16.7 ± 3.7^{Aa}	17.4 ± 4.5^{Aa}	14.8 ± 2.5^{Aa}	15.2 ± 2.4^{Aa}	14.7 ± 2.7^{Aa}	14.0 ± 4.2^{Ab}	11.5 ± 2.8^{Ab}	10.0 ± 4.2^{Ab}
IES	16.9 ± 4.2^{Aa}	17.3 ± 3.7^{Aa}	15.9 ± 4.5^{Aa}	15.3 ± 3.3^{Aa}	13.0 ± 2.6^{Ab}	11.6 ± 3.3^{Bb}	10.7 ± 2.3^{Ab}	10.6 ± 3.5^{Ab}
HSS +IES	15.1 ± 1.5^{Aa}	15.1 ± 3.9^{Aa}	10.4 ± 2.8^{Bb}	9.5 ± 3.6^{Bb}	8.9 ± 2.0^{Bb}	8.2 ± 2.2^{Bb}	6.7 ± 3.1^{Ab}	7.0 ± 3.0^{Ab}
SIG (mEq/L)								
HSS	3.42 ± 4.6^{Bb}	5.4 ± 5.2^{Bb}	-2.5 ± 3.1^{Bb}	-2.8 ± 3.3^{Bb}	2.2 ± 3.3^{Bb}	-1.5 ± 3.7^{Bab}	1.2 ± 3.71^{Aa}	2.4 ± 5.4^{Aa}
IES	3.59 ± 2.6^{Bb}	4.8 ± 5.3^{Bb}	3.5 ± 2.0^{Bb}	3.0 ± 4.4^{Bb}	0.9 ± 3.5^{Bab}	0.40 ± 3.0^{ABa}	1.4 ± 3.2^{Aa}	2.0 ± 4.0^{Aa}
HSS +IES	-3.1 ± 2.4^{Bb}	-3.5 ± 4.2^{Bb}	1.2 ± 4.5^{Aa}	2.2 ± 3.7^{Aa}	2.5 ± 1.7^{Aa}	3.7 ± 2.4^{Aa}	5.4 ± 2.5^{Aa}	5.0 ± 2.4^{Aa}
Degree of lethargy*								
HSS	1.0^{Aa}	1.0^{Aa}	1.0^{Aa}	1.0^{Aa}	1.0^{Aa}	1.0^{Aa}	0.0^{Ab}	0.0^{Ab}
IES	1.0^{Aa}	1.0^{Aa}	1.0^{Aa}	1.0^{Aa}	0.5^{ABb}	0.2^{ABc}	0.0^{Ac}	0.0^{Ac}
HSS +IES	1.2^{Aa}	1.0^{Aa}	1.0^{Aa}	0.8^{Ab}	0.2^{Bc}	0.0^{Bc}	0.0^{Ac}	0.0^{Ac}
Fecal Score*								
HSS	3.0^{Aa}	3.0^{Aa}	3.0^{Aa}	3.0^{Aa}	3.0^{Aa}	3.0^{Aa}	0.5^{Ab}	0.0^{Ab}
IES	3.0^{Aa}	3.0^{Aa}	3.0^{Aa}	3.0^{Aa}	3.0^{Aa}	3.0^{Aa}	0.0^{Bb}	0.0^{Ab}
HSS +IES	3.0^{Aa}	3.0^{Aa}	3.0^{Aa}	3.0^{Aa}	3.0^{Aa}	3.0^{Aa}	0.2^{Bb}	0.0^{Ab}
Body Weight (Kg)								
HSS	29.8 ± 5.1^{Ab}					31.0 ± 5.2^{Ba}	31.9 ± 5.5^{Ba}	33.3 ± 5.7^{Aa}
IES	37.9 ± 8.7^{Ab}	ND	ND	ND	ND	41.0 ± 8.4^{Aa}	41.7 ± 9.0^{Aa}	42.7 ± 8.9^{Aa}
HSS +IES	35.2 ± 6.2^{Ab}					38.6 ± 6.6^{Aa}	38.5 ± 7.0^{Aba}	39.4 ± 7.2^{Aa}

ND = not done.
See Table 2 for key.

previously, but was not considered clinically important.[8] Metabolic acidosis is a common finding in calves with spontaneous diarrhea.[19,20] In addition, the reduction in circulating blood volume associated with dehydration increases production of lactic acid (because of poor tissue perfusion) and limits the ability of the kidneys to excrete hydrogenous ions.[3,17] Severe acidosis also impairs control of brain volume, causing lethargy and coma.[13,14] Changes in acid base balance also were confirmed by a significant increased in anion gap values at Time 0. The anion gap is very useful in categorizing the acid base imbalances.[13,14] An increased anion gap is associated with metabolic acidosis caused by increase in the organic acids (lactic acid and ketoacids).[13] Higher concentrations of L-lactate were observed at Time 0 in all groups (Table 2).

The SIG provides an estimate for the difference among the net strong ion charge of plasma nonvolatile buffers (albumin, globulin, and phosphate), unmeasured strong anion concentrations (L-lactate, D-lactate, sulfate, nonesterified fatty acids, ketoacids, pH-independent phosphate charge, and other strong anions), and unmeasured strong cation concentrations (Ca^{2+}, Mg^{2+}). SIG should be approximately 6 mEq/L. An SIG -3.0 mEq/L indicates an increase in unidentified strong anions.[21] Low values of the strong ion difference are related to conditions of acidosis.[13]

Other studies did not observe metabolic acidosis after induction of diarrhea and dehydration with saccharose, hydrochlorothiazide, spironolactone, and furosemide[10] or saccharose and furosemide.[11] This fact makes it difficult to compare the alkalinizing capacity

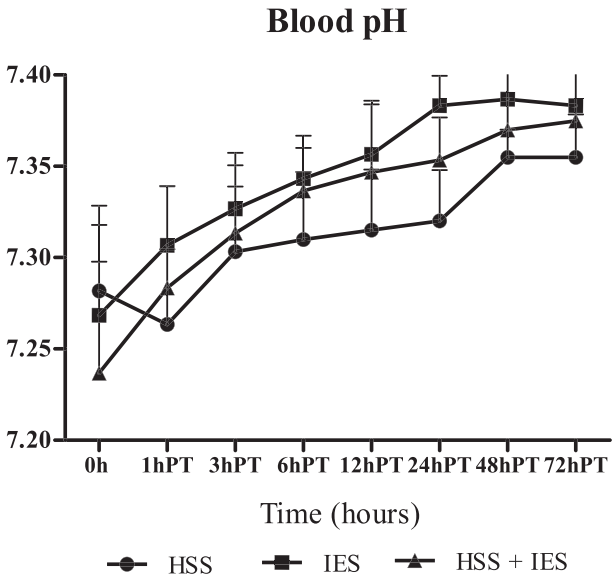

Fig 1. Blood pH in dehydrated calves with diarrhea and response to treatment: hypertonic saline solution (HSS; IV); isotonic electrolyte solution (IES; PO); hypertonic saline solution and isotonic electrolyte solution (HSS + IES).[ab] $P < .05$ compared between groups. 0 hour (48 hours after induction of diarrhea and dehydration). PT (hours after treatment).

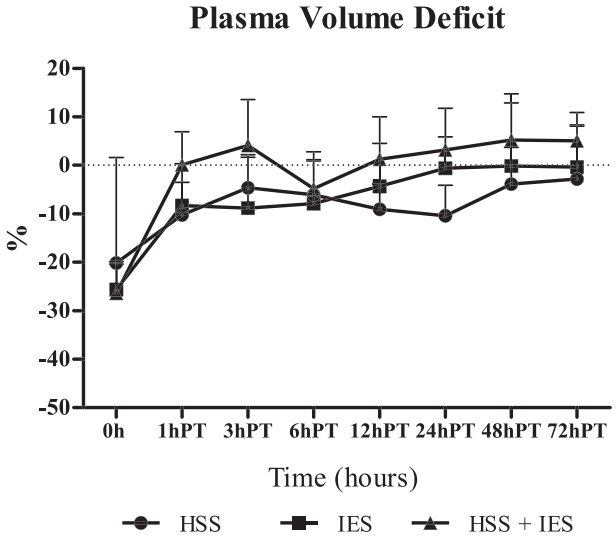

Fig 2. Plasma volume déficit (%) in dehydrated calves with diarrhea. See Figure 1 for key.

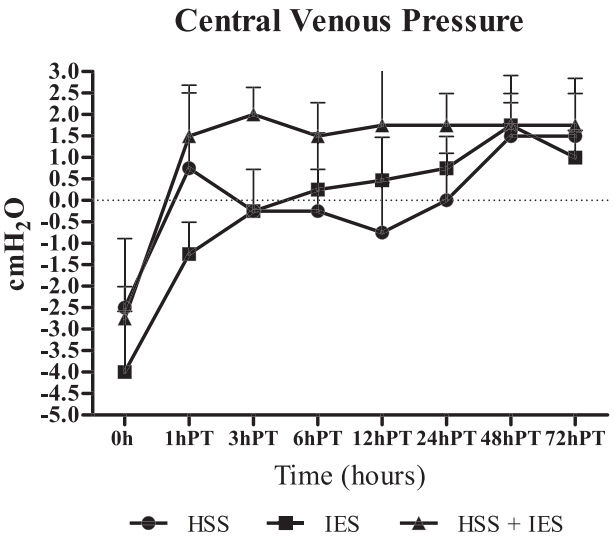

Fig 3. Central venous pressure (cmH_2O) in dehydrated calves with diarrhea. See Figure 1 for key.

of the electrolyte solutions in these experiments. The mechanism by which the diuretic effect of furosemide is produced is by its direct action on renal tubular function. To correct hypovolemia, the body increases reabsorption of sodium. However, to maintain electroneutrality, the sodium reabsorption in the proximal tubule must be accompanied by reabsorption of anions, such as chloride. Because the patient is hypochloremic, a greater amount of sodium reaches the distal tubule, where, under the action of aldosterone, hydrogenous ions are secreted to retain sodium. Renal excretion of hydrogenous ions is directly proportional to bicarbonate reabsorption, giving rise to metabolic alkalosis.[22,23] The main action of hydrochlorothiazide is to increase the urinary excretion of sodium and chloride.[23,24] Spironolactone acts as a specific aldosterone antagonist, primarily by competitive binding of receptors at the aldosterone-dependent sodium potassium exchange site in the distal convoluted renal tubule.[23,24] Spironolactone therefore will antagonize the hypokalemic effect of furosemide and hydrochlorothiazide,[23] but exert a weaker diuretic, natriuretic, and chloruretic effect than furosemide. In this study, the use of higher doses of saccharose, hydrochlorothiazide, and spironolactone caused diarrhea, dehydration, and metabolic acidosis. In the venous circulation, metabolic acidosis has a vasoconstrictive effect, which tends to centralize blood flow and predispose to pulmonary congestion. Acid base abnormalities frequently are present in sick calves.[21] One of the main compensatory effects to decrease the degree of systemic metabolic acidosis is the urinary excretion of hydrogenous ions. Because of the state of dehydration, there is a prominent decrease in urine volume, substantially decreasing the elimination of hydrogenous ions, and responsible for the decreased blood pH.[4,17] The results demonstrate that treatment with IES and IES + HSS were effective in correcting metabolic acidosis by removing excess hydrogen ions, increasing renal flow and buffering by acetate. To be metabolized in the canine liver, acetate requires 2 molecules of hydrogen ions. In a study comparing the effects of oral rehydration with sodium bicarbonate or sodium acetate in calves with spontaneous diarrhea, investigators found that both solutions were capable of treating metabolic acidosis 12 hours after administration.[25] Acetate has an advantage over bicarbonate because it does not alkalinize the abomasal fluid or interfere with the coagulation of milk.[26] Sodium

acetate also stimulates the absorption of water in the small intestine[27] and is easily metabolized by peripheral tissues.[26] The calves in this study continued to receive saccharose along with milk during the treatment phase. Studies in calves with spontaneous diarrhea[2] and diarrhea induced by *Escherichia coli*[27] showed that metabolic acidosis can cause a decrease in pCO_2. One form of compensation during metabolic acidosis is an increase in ventilation and a consequent decrease in pCO_2.[13] However, this compensation was brief, and metabolic acidosis can persist for more than 24 hours before any sign of respiratory compensation. The lack of change in pCO_2 after induction of diarrhea may be because of the fact that measurements during this period were taken at relatively large intervals and the animals could have shown signs of respiratory compensation during the time periods between measurements. The current recommended treatment for moderately dehydrated diarrheic calves is PO electrolyte administration alone, whereas combined administration of fluids IV and PO electrolyte administration is a fundamental requirement for treating severely dehydrated diarrheic calves.[6] Traditional isotonic fluid administration is difficult and expensive to accomplish in the field, requiring venous catheterization, large volumes of isotonic fluid, and periodic monitoring.[7,10]

Fluids with low osmolality (300 mOsm/kg) have inadequate energy content because they have insufficient glucose. If the electrolyte is supplied without concomitant milk it is recommended to use a high osmolality solution (600 mOsm/L).[20] Although we did not offer milk to the calves during treatment, the association of IES + HSS may have increased the absorption of glucose from the isotonic electrolyte solution, causing glucose concentrations to remain similar to those at Time 0, which did not occur in other groups where there was a decrease in glucose concentrations after treatment.

The treatment of osmotic diarrhea and dehydration with HSS, IES, or HSS + IES (Table 3) was not able to change the consistency of feces. In a study of calves with diarrhea induced by coronavirus or rotavirus, the animals showed marked improvement in fecal consistency after fluid therapy, but did not experience adequate recovery of plasma volume compared with calves that continued to have watery diarrhea.[28] These data reinforce the observations in humans that improvement in fecal consistency is not a guide for evaluating fluid therapy.[29] In addition, rehydration can increase the ability of human patients to produce watery feces.[30]

Twenty-four hours after treatment, animals receiving the HSS treatment alone still showed signs of dehydration, lethargy and metabolic acidosis. As such, treatment with HSS solution alone is not effective for the treatment of induced osmotic diarrhea in calves. The use of HSS IV combined with a PO electrolyte solution is effective in the treatment of calves with noninfectious diarrhea, dehydration, and metabolic acidosis.

Footnotes

[b] ECG 6 Ecafix Indústria e Comércio Ltda, São Paulo, Brazil
[c] Sonosite 180 Plus-version 1.9- Sonoma Health Products, Forestville, CA
[d] Becton Dickinson, São Paulo, Brazil
[e] Liquemine, Laboratório Roche, São Paulo, Brazil
[f] Itambe Laticínios, Belo Horizonte, Minas Gerais, Brazil
[g] Aldactone, Laboratórios Pfizer Ltda, Guarulhos, São Paulo, Brazil
[h] Sanofi, Synthelabo Ltda, Rio de Janeiro, Brazil
[i] CELM Cia. Equipadora de Laboratórios Modernos, Barurei, São Paulo, Brazil
[j] Modelo Lyasis Laboratory Equipment & Supplies, Milão, Italy
[k] AVL Omni GMI Instrumental, Copenhagen, Denmark
[l] Ecafix Indústria e Comércio Ltda
[m] Software SAS para Estatística e Análise de Dados
[a] Itambé Laticínios, Belo Horizonte

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