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RESEARCH ARTICLE

Serum Potassium-Lowering Effects of Insulin Plus Dextrose and Adrenalin Treatment that Enhance Intracellular Potassium Transitions in Hyperkalemic Diarrheic Calves

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ABSTRACT

The study examined the serum potassium-lowering effects of different treatment options for hyperkalemia in diarrheic calves (n=18). Calves were allocated into three treatment groups. All groups received isotonic sodium bicarbonate solution for a period of 90 minutes. The animals in group 1 received no further treatment, those in group 2 received a further dose of 50% dextrose and insulin, and those in group 3 received a further dose of adrenaline. High serum K levels in all groups significantly decreased after treatment (AT) than before treatment (BT). Serum potassium levels AT in groups 2 and 3 were found to be significantly lower than those in group 1. Increase in pH, bicarbonate and total carbon dioxide values were observed AT in all groups. However, bicarbonate and total carbon dioxide levels in the AT were not statistically significantly different from those in the adrenaline group compared with the groups 1. These parameters were significantly lower in the group 2. Moreover, the concentration of glucose in the groups 2 in contrast to the adrenalin group was higher than that in both the BT and group 1 AT. The insulin + dextrose combination and adrenaline applications in hyperkalemic calves had similar effects. However, the administration of adrenaline had a lower negative effect on metabolic acidosis treatment.

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INTRODUCTION

Neonatal calf diarrhoea is an important disease with high morbidity and mortality as it causes serious economic losses (Tajik and Nazifi, 2013; Meganck *et al.,* 2014; Zafar *et al.,* 2015; Avci *et al.,* 2015). The most common causes of calf deaths are metabolic acidosis and hyperkalemia (Divers and Peek, 2008).

In calves with diarrhoea, the absorption of fluid–electrolytes and organic molecules from the intestines decreases as the loss of fluid–electrolytes particularly sodium (Na^{++}), bicarbonate (HCO_3) and potassium (K^+) increases. Therefore, fluid that accumulates in the intestines is excreted, and increased hemoconcentration, hyperkalemia and subsequently acute renal failure occur (Constable and Grünberg, 2013). Bicarbonate deficit and metabolic acidosis occur because of the loss of fluid-electrolytes. Furthermore, intracellular and extracellular acidosis occurs, and the passage of hydrogen from the extracellular compartment to the intracellular compartment increases. To balance this condition, the movement of intracellular K^+ out of the cells and the movement of extracellular Na^{++} into the cells increase and cause hyperkalemia (Berchtold, 2009). In calves with diarrhoea, death is inevitable when no proper treatment is administered for acute renal failure, metabolic acidosis and hyperkalemia (Constable and Grünberg, 2013; Meganck *et al.,* 2014; Merwad *et al*., 2015).

Isotonic or hypertonic sodium chloride (NaCl) is commonly used in rehydration treatment. The intravenous administration of isotonic or hypertonic HCO_3 is a widely used treatment against metabolic acidosis (Koch and Kaske, 2008; Coşkun *et al.,* 2010). A combined fluid treatment is also common, in which the calculated fluid

requirement is accounted for by using isotonic NaCl and the base deficit is addressed by using HCO_3 (Berchtold, 2009).

The remedy for hyperkalemia involves the treatment of the primary disorder that causes hyperkalemia to ensure the entry of K into the cells and the excretion of excess potassium (Kimberley and Greenberg, 2005). The administration of insulin + glucose, β_2- adrenergic agonists and sodium bicarbonate ($NaHCO_3$) is recommended to accelerate the re-entry of extracellular K (Weisberg, 2008). Although HCO_3 infusions have been reported to reduce high K levels in calves with diarrhoea (Coşkun *et al.,* 2010; Özkan *et al.,* 2011), HCO_3 should not be used as mono therapy, particularly in life-threatening, severe hyperkalemia (Kimberley and Greenberg, 2005). Moreover, HCO_3 has been reported to be unusable in the emergency treatment of hyperkalemia (Weisberg, 2008). The administration of both insulin and β_2- adrenergic agonists stimulates the Na-K-ATPase pumps in the cell, thus accelerating the entry of K into the cells. However, as the administration of insulin in diarrheic calves causes hypoglycaemia, its administration without supplemental glucose is not recommended (Constable and Grünberg, 2013). Moreover, it is expressed that β_2- adrenergic agonists should not be used as monotherapy (Kim, 1996).

Fluid therapy against hypovolemia in calves with diarrhoea and intravenous isotonic bicarbonate solution (ISBS) against metabolic acidosis and hyperkalemia are routine treatment methods (Coşkun *et al.,* 2010). Although hyperkalemia can be treated effectively with options that ensure the entry of extracellular K in human medicine (Kimberley and Greenberg, 2005), no study has demonstrated the efficacy of these practices in hyperkalemia treatment in calves with diarrhoea. This study aimed to determine the K-reducing effect of adrenaline, insulin and dextrose in addition to intravenous ISBS administration in hyperkalemic calves with diarrhoea, using clinical and laboratory findings.

MATERIALS AND METHODS

Animal materials: This study was performed on calves that were brought to the clinic at the Department of Internal Medicine of Yuzuncu Yil University, Faculty of Veterinary Medicine with symptoms of diarrhoea or those that were locally obtained with hyperkalemic diarrhoea (Ethics Protocol No: 19.04.2012–2012/03). Animal material consisted of six healthy (control group) calves (Simmental n=3, Brown Swiss n=3), and 18 Simmental and Brown Swiss calves with hyperkalemic diarrhoea, age ranging from 2 to 30 days and live weight of 20 to 35 kg.

Study design and treatment: Hyperkalemia were assessed according to the serum K levels. In this study, diarrheic calves with serum K^+ concentrations higher than 5.8 mmol /L were considered hyperkalemic as reported by Trefz *et al.* (2013). Hyperkalemic calves (n=18) were allocated into three groups (n=6), with each group's mean K concentration being higher than 7.0 mmol/L. First, fluid requirements and HCO_3 deficit of the calves were calculated according to the formulas. Afterwards, 1.3% ISBS was administered in doses 40 mL/kg/h to all groups during the study period (90 min) for treatment. The animals in group 1 received fluid–electrolyte treatment only. Those in group 2 received a further dose of 50% dextrose (1 mL/kg, i.v. infusion, once, for a period of 5 min) and insulin (Novorapid®Flexpen®, Novo Nordisk™ Co., Turkey) (0.25 IU/kg, S/C, once), and those in group 3 received a further dose of adrenaline (Biofarma™ Drug Co., Turkey) (0.01 mg/kg i.v., once, slow administration). The remaining concentrations of ISBS were administered to all groups for 90 min at the end of the sampling (after 90 min).

Blood Sampling: Blood samples were taken via the vena jugularis before treatment (BT) and 90 min after treatment (AT) from calves with diarrhoea and once from the control group. For haematological, biochemical and blood gas analyses were taken into tubes with EDTA, tubes without anticoagulant and sterile injectors with lithium heparin, respectively.

Laboratory analysis: Haematological analyses were performed using a veterinary haematology device (QBCvetautoreader®-Idexx™, UK). Blood samples obtained for biochemical analyses were centrifuged at 4000 rpm for 10 min with centrifuge device (Rotofix 32®-Hettich™, Germany). Serum that was obtained after centrifuging was transferred into serum storage tubes. Serum Na, K and chlorine (Cl) levels were analysed using an ion selective device (Medica®-ISE, USA). Serum samples were kept under -20°C until other biochemical analyses [total protein (TP), albumin, glucose, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK)] were measured using a spectrophotometer (Photometer® 5010, Boehringer Mannheim™, Germany) according to the procedures outlined in commercial test kits (Randox™, UK). Blood gas analyses [power of hydrogen (pH), partial pressure of carbon dioxide (PCO_2), HCO_3, anion gap (AnGAP), total carbon dioxide (TCO_2), partial pressure of oxygen (PO_2)] were measured using a portable veterinary blood gas device (VetStat®-İdexx™, UK) following sampling.

Statistical analysis: Data was not normally distributed. Therefore, non-parametric Mann Whitney U test was performed to compare two independent group mean ranks (Control vs each hyperkalemic groups). Wilcoxon test was used to see if there was a difference between two dependent group means (before and after treatments). Kruskal Wallis test was used to see if there was a difference among group means (3 groups including treatment option). If the Kruskal Wallis test detected a difference among groups then the groups were compared in pairs using Mann Whitney U test. Statistical significance was determined to be $P<0.05$. For this purpose, the SPSS 16.0 software was used (SPSS Inc., Chicago, IL, USA). All data were given as arithmetic mean±SEM.

RESULTS

Hematological, biochemical, electrolyte and blood gas findings of calves with hyperkalemic diarrhoea are given in Tables 1 to 3.

Table 1: Haematological results of calves with hyperkalemic diarrhoea (mean±SEM)

Parameters		Control	Hyperkalemic Diarrheic Calves		
			Group 1	Group 2	Group 3
Hct	BT	38.4±2.46[a]	44.2±3.39[b]	48.5±3.18[b]	50.9±3.08[b]
(%)	AT		34.1±2.91*	31.6±3.60*	36.9±1.79*
Hb	BT	12.6±0.58[a]	14.9±1.07[b]	15.9±0.72[b]	17.0±1.22[b]
(mg/ dL)	AT		12.2±1.36*	10.2±0.99*	13.1±0.76*
WBC	BT	10.9±0.66[a]	18.3±2.57[b]	18.4±3.05[b]	17.7±3.96[b]
(10^9/L)	AT		14.3±1.83[b]*	15.1±3.21[b]*	13.8±3.19[b]*
GRANS	BT	4.14±1.13[a]	8.38±1.87[b]	7.10±2.21[b]	7.68±4.09[b]
(10^9/L)	AT		6.42±1.92	6.06±1.11	5.29±2.59
L/M	BT	6.76±1.63	9.80±1.42	11.3±2.85	10.0±2.10
(10^9/L)	AT		7.88±1.91	9.04±2.33	8.51±1.28
PLT	BT	685.0±49.6	703.2±136.7	714.3±59.7	692.0±147.2
(10^9/L)	AT		548.4±122.7	644.7±72.2	555.0±106.9

In each group: n=6. Statistical significance (P<0.05) with different letters in the same row. Statistical significance of a parameter BT and AT: *P<0.05. L/M: lymphocyte+monocyte, PLT: platelet.

Table 2: Biochemical results of calves with hyperkalemic diarrhoea (mean±SEM).

Parameters		Control	Hyperkalemic Diarrheic Calves		
			Group 1	Group 2	Group 3
TP	BT	7.30±0.37[a]	6.50±0.42	6.94±0.64	7.06±1.05
(g/ dL)	AT		4.96±0.48[b]*	4.74±0.75[b]*	4.86±0.62[b]*
Albumin	BT	3.28±0.16[a]	3.32±0.19	3.68±0.12	3.04±0.24
(g/dL)	AT		2.49±0.33[b]*	2.52±0.25[b]*	2.08±0.19[b]*
Glucose	BT	67.4±8.37[a]	75.6±13.5	72.1±8.46	77.1±14.3
(g/ dL)	AT		69.9±12.6[a]	149.1±20.5[b]*	106.1±18.3[ab]
BUN	BT	8.4±1.01[a]	40.4±2.03[b]	57.2±2.11[b]	38.1±3.19[b]
(mg/ dL)	AT		35.6±1.99[b]	46.4±1.06[b]*	32.5±2.74[b]
Creatinine	BT	0.98±0.11[a]	3.30±0.87[b]	3.90±0.50[b]	3.28±0.82[b]
(mg/dL)	AT		2.76±0.58[b]	3.08±0.48[b]*	2.76±0.72[b]
AST	BT	83.2±9.01	59.5±9.89	68.1±8.83	53.6±19.0
(U/L)	AT		58.5±11.5	58.4±6.18	56.6±23.4
ALT	BT	18.6±3.57	29.9±7.15	23.4±6.01	17.2±9.63
(U/L)	AT		27.7±6.07	23.3±1.95	20.2±9.0
LDH	BT	1335±212.9	1711±133.8	2200±175.6	1830±416.4
(U/L)	AT		1624±198.4	1673±96.7	1545±350.6
CK	BT	185.3±20.1	540±15.4	623±16.2	638±41.6
(U/L)	AT		836±37.9	714±20.3	939±74.9

In each group: n=6. Statistical significance (P<0.05) with different letters in the same row. Statistical significance of a parameter BT and AT: *P<0.05.

Table 3: Electrolyte and blood gas results of calves with hyperkalemic diarrhoea (mean±SEM).

Parameters		Control	Hyperkalemic Diarrheic Calves		
			Group 1	Group 2	Group 3
K	BT	4.38±0.06[a]	7.24±0.71[b]	7.30±0.52[b]	7.40±0.39[b]
(mmol/L)	AT		5.54±0.39[b]	4.58±0.39[a]*	4.42±0.18[a]*
Na	BT	140.6±0.68[a]	126.2±3.15	131.4±3.34[b]	129.8±3.81[b]
(mmol/L)	AT		137.6±3.08*	138.2±3.62*	138.4±2.11*
Cl	BT	100.4±0.68	98.4±4.12	104.8±3.15	102.4±2.23
(mmol/L)	AT		101.7±2.24	103.2±2.95	103.8±2.49
pH	BT	7.45±0.01[a]	7.24±0.04[b]	7.11±0.05[b]	7.23±0.07[b]
	AT		7.35±0.04[b]	7.27±0.02[b]*	7.29±0.04[b]
PO_2	BT	30.0±0.84	33.4±1.03	27.6±3.12	27.5±6.58
(mm/Hg)	AT		32.3±1.44	35.0±1.73*	32.2±2.36
PCO_2	BT	47.8±1.80	44.4±4.62	50.8±5.95	49.0±5.87
(mm/Hg)	AT		50.2±4.03	44.6±2.65	50.2±2.56
HCO_3	BT	30.7±1.03[a]	18.2±2.20[b]	14.6±1.22[b]	19.4±3.71[b]
(mmol/L)	AT		26.3±4.52[ab]	18.9±1.15[b]	22.3±2.54[ab]
TCO_2	BT	32.1±1.08[a]	19.4±4.50[b]	16.0±1.28[b]	20.7±3.75[b]
(mmol/L)	AT		27.8±4.58[ab]	20.2±2.21[b]	23.7±2.59[ab]
AnGAP	BT	13.9±0.83	18.5±3.18	19.3±1.33	18.0±2.50
(mmol/L)	AT		16.6±4.59	16.5±1.54	16.7±2.20

In each group: n=6. Statistical significance (P<0.05) with different letters in the same row. Statistical significance of a parameter BT and AT: *P<0.05.

Hematological findings: Hct, Hb concentration, WBC and granulocyte (GRANS) (P<0.05) were high in all groups BT compared with those in the control group. After treatment, Hct, Hb and GRANS decreased in all groups, showing no difference from those in the control group. However, WBC in AT was still higher than that in the control group (P<0.05) despite the fact that it decreased AT compared with that BT (P<0.05). When the date before and after treatment were compared significant decreases in HCT and HGB (P<0.05) in all groups, whereas a non-significant decreases in GRANS were observed. Other haematological parameters; lymphocyte/ monocyte (L/M) and PLT counts were not statistically significant (Table 1).

Biochemical findings: Total protein (TP) and albumin levels were not statistically significant in BT compared to the control group, whereas this parameters decreased in all groups AT compared with those in the control group and BT. Blood urea nitrogen (BUN) and creatinine (P<0.05) levels were high in all groups BT. Despite the fact that these levels decreased in all groups AT, only the decreased values in group 2 was significant compared with those BT (P<0.05). Furthermore, BUN and creatinine (P<0.05) levels were still high AT compared with those in the control group. Glucose levels in all groups were not significant in BT compared to the control groups. Similarly its levels in group 1 and 3 were not significant in AT compared to the control group and BT. However, glucose levels were increased after treatment compared to before treatment in group 2. Moreover, this increase in group 2 was also statistically significant in comparison with the controls and group 1. Other biochemical parameters; AST, ALT, LDH and CK were not significant (Table 2).

Electrolyte and blood gas findings: The level of K (P<0.05) was found to be high, whereas the level of Na (P<0.05) was found to be low in all groups BT. However, the decrease in K level (except group 1) and the increase in the Na level were significant (P<0.05) AT. The levels of K in groups 1 was higher than those in the control group and groups 2 and 3 (P<0.05) (Table 3).

pH, HCO_3 and TCO_2 (P<0.05) levels were low in all groups BT. Aside from the increase AT, pH (P<0.05) levels were low in all treatment groups, and HCO_3 (P<0.05) and TCO_2 levels (P<0.05) was low in groups 2 compared with those in the control group. The increase in pH and PO_2 (P<0.05) levels were only significant in group 2 AT compared with those BT. However, no statistically significant difference was found in the groups AT. Other parameters; Cl, PCO_2 and AnGAP were not significant (Table 3).

DISCUSSION

The finding that WBC and GRANS counts are high in calves BT is similar to that in previous studies (Niaz *et al.*, 2000; Brar *et al.*, 2015). As reported by Brar *et al.* (2015), it can be interpreted as neutrophilic leucocytosis, which demonstrates an inflammatory reaction.

Similar to the findings of other researchers (Seifi *et al.*, 2006; Kumar *et al.*, 2010), the increase in Hct, Hb, BUN and creatinine levels BT of calves with hyperkalemic diarrhoea in the present study can be interpreted as haemoconcentration caused by dehydration, hypovolemia and decreased glomerular filtration rate

(Dratwa-Chałupnik *et al.,* 2012). Similar to previous studies (Bleul *et al.,* 2005; Zilaitis *et al.,* 2015), the decrease in Hct, Hb, WBC, GRANS, TP, albumin, BUN and creatinine levels AT (Tables 1, 2) can be related to dilution following fluid therapy and response to treatment (Coskun *et al.,* 2010; Trefz *et al.,* 2012; Zilaitis *et al.,* 2015). However, despite the decrease AT, WBC, BUN and creatinine levels remaining high may be attributed to the uncompleted treatment process as stated by the Koch and Kaske (2008).

Metabolic acidosis is defined as the condition in which the venous blood pH is lower than 7.28 and the HCO_3 ion (Kasari, 1999) and TCO_2 (Groutides and Michell, 1990b) concentrations are lower than 20 mmol/L. In this study, the fact that pH, HCO_3 and TCO_2 levels were low in all groups BT compared with those in the control groups demonstrates metabolic acidosis in accordance with the literature (Sobiech *et al.,* 2013). Many researchers have reported that solution with sodium bicarbonate (isotonic or hypertonic) is the most important buffer for the treatment of metabolic acidosis in calves with diarrhea (Berchtold, 2009). Similarly to these researchers, metabolic acidosis tended to disappear AT, and pH, HCO_3 and TCO_2 levels remained lower than those in the control group. However, acidemia in calves was not fully recovered. This condition may be due to the fact that the treatment continued at the time of sampling in similar to Coşkun *et al.* (2010) findings.

$NaHCO_3$ infusion increases blood pH, thus ensuring the entry of extracellular K into the cells (Constable and Grünberg, 2013). Similarly, in the current study, serum K levels decreased in all groups AT (Table 3). This finding is in accordance with the finding that ISBS has a hypokalemic effect in the treatment of hyperkalemia because of metabolic acidosis in calves (Özkan *et al.,* 2011). The decrease in K level in AT compared with that in BT was a statistically significant in group 2 and 3; but it was found to be high ($P<0.05$) only in group 1 which was administered ISBS, compared with the control group and other groups AT. However, a statistically significant decrease was found in all groups AT. This finding is similar to that of Kimberley and Greenberg (2005), who stated that the hyperkalemic effect of ISBS in acute severe hyperkalemia occurs in a long period of time. These findings support those of some researchers (Kimberley and Greenberg, 2005; Weisberg, 2008) who found that $NaHCO_3$ should not be used as monotherapy for the emergency treatment of life-threatening hyperkalemia.

In the treatment of hyperkalemia in human medicine it is recommended to administrate $NaHCO_3$ and insulin plus dextrose for accelerate the re-entry into cells in K (Weisberg, 2008). Insulin accelerates the entry of K into the cells by stimulating Na-K-ATPase activity. However, insulin administration without supplemental glucose is not recommended in calves, because its administration may lead to hypoglycemia (Constable and Grünberg, 2013). In this study, serum K levels decreased significantly in groups 2 than in the group 1 (Table 3). This condition shows that the combined treatments with dextrose plus insulin in addition to ISBS are more effective in reducing serum K levels. These findings concur with those of Trefz *et al.* (2015), who suggest that combination of sodium bicarbonate and glucose solution might also be advantageous for hyperkalemia treatment in calves with diarrhoea. This effect is reported to be due to increased endogenous insulin because of dextrose application (Trefz *et al.,* 2015) even though they did not use insulin therapy in addition to dextrose contrary to the present study. Therefore, further studies in hyperkalemic calves should be made for determination of the relationship between reduction of K and application of exogenous insulin without supplemental dextrose.

In this study, K concentrations were significantly low in the group that received adrenaline in addition to ISBS compared with the group that received only ISBS (group 1). These findings are similar to those of many researchers (Cohn *et al.,* 2000; Clausen, 2010) who found that catecholamine's reduce K levels. Plasma epinephrine levels have been reported to remain the same before and after hypertonic $NaHCO_3$ treatment (Kim, 1996). Therefore, this study demonstrates that the administration of additional adrenaline at a basal level to hyperkalemic calves causes an apparent reduction in serum K levels.

Isotonic HCO_3 infusions do not cause important changes in serum glucose concentrations (Coşkun *et al.,* 2010). Similar to the aforementioned findings, the current study found that serum glucose levels were not statistically different AT in the groups (1 and 3) that did not receive dextrose treatment in addition to ISBS. Contrary to the findings suggesting that the addition of glucose to intravenous solutions does not change the plasma glucose levels (Groutides and Michell, 1990a), this study found that the serum glucose concentrations AT were higher in the groups 2 that received dextrose in addition to ISBS than those BT in other groups (control, groups 1 and 3). These findings agree with those of Grünberg *et al.* (2011); who stated that orally administered glucose and HCO_3 + glucose combination lead to a 2h increase in the plasma glucose concentration in healthy calves.

The addition of glucose to solutions that contain Na, Cl and HCO_3 does not have any other advantage but to reduce hyperkalemia. However, the addition of glucose reduces the effectiveness of solutions in reducing acidosis (Groutides and Michell, 1990a). Similar to the findings of some researchers (Groutides and Michell, 1990a; Kim, 1996), despite an increase observed in some parameters (HCO_3 and TCO_2) that indicate metabolic acidosis AT than BT in the group 2 that received glucose aside from ISBS, these parameters were lower than those in the control group. This condition demonstrates that additional $NaHCO_3$ treatment is necessary to correct the base deficit under circumstances in which dextrose is added to i.v. solutions in calves with diarrhoea (Berchtold, 2009).

In this study, HCO_3 and TCO_2 levels AT in group 2 that received dextrose aside from ISBS were low at a statistically significant level compared with those in the control group. No statistically significant difference was found in the group that received adrenaline compared with the control group and group 1. From these results it is understood that adrenaline treatment has lesser negative effects on the restoration of acidosis than dextrose treatment. Furthermore, serum glucose concentrations did not have a statistical difference in group 3 compared with the control group and group 1, unlike in the groups that received dextrose AT. Ponnampalam *et al.* (2012)

determined that epinephrine injection increases blood glucose levels in lambs via β-adrenergic stimulation. Therefore, despite the fact that HCO_3 and TCO_2 levels were not significantly different in the groups that received adrenaline, the relatively lower levels of these substances occurring AT compared with those in the control group and the groups that received bicarbonate may be due to the relative increase in serum glucose concentrations AT, consistent with the findings of Ponnampalam *et al.* (2012).

Conclusions: As a result, despite all treatments being effective in reducing serum K levels in calves with severe hyperkalemic diarrhoea, only ISBS treatments was found to have a lower effect than other treatment regimes. Insulin–dextrose and adrenaline treatments, aside from isotonic $NaHCO_3$ solution, were similarly shown to reduce serum K levels and could be used successfully in the treatment of hyperkalemia. Furthermore, adrenaline treatment in addition to ISBS had lesser negative effects in the treatment of metabolic acidosis compared with insulin + dextrose, and is thus more safe and practical.

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