The relationship between the severity of azotemia and blood gases in 101 calves with neonatal diarrhea

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AYDOĞDU, U., A. COŞKUN, O. BAŞBUĞ, S. TÜRK, Z. T. AĞAOĞLU: The relationship between the severity of azotemia and blood gases in 101 calves with neonatal diarrhea. Vet. Arhiv 93, 31-38 2023.

ABSTRACT

The aim of this study was to determine the relationship between the severity of azotemia and blood gas parameters in 101 neonatal calves with diarrhea. The calves were divided into 3 groups on the basis of their creatinine levels. The 3 groups were defined as: the non-azotemia group (<2.00 mg/dL), the mild-moderate azotemia group (2.01-5.00 mg/dL), and the severe azotemia group (>5.01 mg/dL). Azotemia was not detected in 35 of the 101 calves with diarrhea, mild-moderate azotemia was identified in 34, and severe azotemia in 32. Blood pH was significantly lower in the severe azotemia group compared to the non-azotemia and mild-moderate azotemia groups, while K and lactate levels were significantly higher. Although the HCO_3^- and BE values of the severe azotemia group were lower than the other groups, a statistical difference was only found with the mild-moderate azotemia group. Ionized calcium (iCa^{+2}) level was also lower in the severe azotemia group compared to the other groups, but the difference was only significant with the non-azotemia group. In conclusion, it was observed that azotemia is a common occurrence in neonatal calves with diarrhea, and there is a significant relationship between the severity of azotemia and blood gases. Therefore, it may be concluded that it would be beneficial to monitor renal functions during the treatment of calves with neonatal diarrhea.

Key words: azotemia; calf; diarrhea; blood gases

Introduction

Neonatal calf diarrhea is one of the most common causes of morbidity and mortality in cattle farms, and is also significantly responsible for economic losses (DONOVAN et al., 1998; MEGANCK et al., 2014). Dehydration occurs in calves with diarrhea due to the loss of water with faeces and the decrease or absence of milk consumption. At the same time, the loss of HCO_3^-, Na^+, Cl^- and K^+ occurs with the stool, and thus metabolic acidosis and various electrolyte disorders occur (AYDOGDU et al., 2018; AYDOGDU et al., 2019; COSKUN et al., 2020b; TREFZ et al., 2012). In calves with diarrhea, due to dehydration, renal perfusion decreases and renal function is adversely affected. The main reason for the deterioration in renal function is the decrease in arterial blood pressure and glomerular

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ISSN 0372-5480
Printed in Croatia

filtration rate due to dehydration (BAŞER and CİVELEK 2013; CONSTABLE et al., 2018). GUZELBEKTES et al. (2007) reported that, as the severity of dehydration increases, the severity of azotemia increases in calves with diarrhea. If dehydration is not corrected or if insufficient fluid treatment is applied, renal damage may become permanent and cause death (BAŞAK et al., 1991; KIYKIM, 2006; PORTILLA and SHAH, 2010). Determination of the serum creatinine level is an important parameter used to reveal the glomerular filtration rate (ASHLEY and MORLIDGE, 2008; CONSTABLE et al., 2018).

Although it has been reported that azotemia occurs in calves with diarrhea due to dehydration, to our knowledge no research has been conducted to classify calves with neonatal diarrhea according to azotemia severity and its relationship with blood gas parameters. Hence, the aim of this study was to determine the prevalence of azotemia in calves with neonatal diarrhea, and the relationship between the severity of azotemia and blood gas parameters.

Materials and methods

A total of 101 neonatal calves (<30 days) of different breeds and genders, all with symptoms of diarrhea, were allocated for this study. All the animals were admitted to the Sivas Cumhuriyet University, Faculty of Veterinary Medicine, Animal Hospital, for examination and treatment. Blood samples were collected from the jugular vein into syringes without anticoagulant, and analyses were preformed immediately using a portable blood gas analyzer (Epoc, Canada). The following parameters were analyzed: Blood pH, pCO2, HCO3-, BE, Na+, K+, iCa+2, Cl-, lactate and creatinine.

The calves were divided into 3 groups on the basis of creatinine levels. In determining the group definitions, a classification used for cats and dogs (BROWN, 2013) was modified and adapted for calves using cattle reference values (CONSTABLE et al., 2018). The 3 groups are defined as: the non-azotemia group (<2.00 mg/dL), the mild-moderate azotemia group (2.01-5.00 mg/dL), and the severe azotemia group (>5.01 mg/dL). Azotemia was not detected in 35 of the 101 calves with diarrhea, mild-moderate azotemia was identified in 34, and severe azotemia in 32.

Statistical analysis. The data from the study are presented as mean and standard error of the mean (Mean±SEM). One-way analysis of variance was used to determine the differences between groups. The relationship between the creatinine level of calves and blood gas parameters was found using Pearson's correlation. The level of statistical significance was taken as P<0.05. Statistical analyses were performed using the SPSS program (Version 22).

Results

Metabolic acidosis (low pH, HCO_3^- and BE) was present in the calves with diarrhea. Changes in blood gas parameters, according to the severity of azotemia in the calves with neonatal diarrhea are given in Table 1. Blood pH was significantly lower (P <0.05) in the severe azotemia group compared to the non-azotemia and mild-moderate azotemia groups, while the K^+ and lactate levels were significantly higher (P <0.05). Although the HCO3 and BE values of the severe azotemia group were lower than the other two groups, a statistical difference was only found in the mild-moderate azotemia group. The iCa^{+2} level was also lower in the severe azotemia group compared to the other groups, but the difference was only significant with the non-azotemia group.

After examining the relationship between creatinine levels and blood gas parameters of calves with neonatal diarrhea, it was determined that the animal's level of creatinine was negatively correlated with pH, BE, Na^+ and iCa^+2, and positively correlated with K^+ and lactate.

Table 1. Changes in blood gas parameters according to the severity of azotemia

Parameters	Non-Azotemia (<2 mg/dL) n=35	Mild-Moderate Azotemia (2.01-5.00 mg/dL) n=34	Severe Azotemia (>5.01 mg/dL) n=32
pH	7.26±0.03[a]	7.24±0.02[a]	7.13±0.03[b]
pCO_2	41.09±1.80	49.45±2.09	48.21±3.46
HCO_3^-	20.49±1.45[ab]	23.20±1.53[a]	17.90±1.40[b]
BE	-6.28±1.86[ab]	-4.73±1.89[a]	-11.45±1.81[b]
Na^+	134.57±1.33	134.52±1.40	130.12±1.32
K^+	4.61±0.12[c]	5.44±0.19[b]	6.82±0.34[a]
iCa^{+2}	1.30±0.02[a]	1.25±0.02[ab]	1.16±0.04[b]
Cl^-	101.94±1.54	100.32±1.42	99.25±1.73
Lactate	2.11±0.32[b]	3.48±0.52[b]	5.97±0.70[a]
Creatinine	1.46±0.05[c]	2.98±0.12[b]	8.19±0.50[a]

pH: concentration of hydrogen ions, pCO_2: partial pressure of carbon dioxide, HCO_3^-: bicarbonate concentration, BE: base excess, Na^+; sodium, K^+; potassium, iCa^{2+}; ionized calcium, Cl^-: chloride. Different letters in the same rows (a,b,c) are statistically significant ($P<0.05$)

Table 2. Level of correlation between creatinine level and blood gas parameters

	pH	pCO_2	HCO_3^-	BE	Na^+	K^+	iCa^{+2}	Cl^-	Lactate
Creatinine	-,254*	,117	-,174	-,215*	-,210*	,553**	-,299**	-,061	,381**

pH: concentration of hydrogen ions, pCO_2: partial pressure of carbon dioxide, HCO_3^-: bicarbonate concentration, BE: base excess, Na^+; sodium, K^+; potassium, iCa^{2+}; ionized calcium, Cl^-: chloride. *Correlation is significant at the level of 0.05 (2-tailed). **Correlation is significant at the level of 0.01 (2-tailed).

Discussion

Excessive loss of water and electrolytes through the gastrointestinal tract during diarrhea is the most common cause of dehydration, which in acute cases, can lead to death. The dehydration process is accompanied by decreases in extracellular fluid and/or intracellular fluid, circulating blood volume, water and electrolyte imbalance (DRATWA-CHAUPNIK et al., 2012). Dehydration and hypovolemia are not synonymous and therefore should not be confused. Dehydration describes water deficiency in the interstitial and intracellular compartments, while hypovolemia pertains to fluid loss in the intravascular space (HUGHSTON, 2016). One of the causes of death and productivity losses in calves with neonatal diarrhea is permanent damage to renal function. In calves with diarrhea, blood flow to the kidneys is reduced due to hypovolemia and the accompanying fluid loss, which can adversely affect kidney function. Prerenal azotemia is a common condition in calves with diarrhea resulting in dehydration, and the treatment is correcting the hypovolemia with adequate and necessary fluid administration at the appropriate time. Studies have shown that prerenal azotemia can be improved with fluid administration (CONSTABLE et al., 2001; ŽILAITIS et al., 2015). LEE et al. (2020) reported that 63.6% of calves with diarrhea had azotemia. In addition to dehydration associated with sepsis (AYDOGDU et al., 2018; KIRBAS et al., 2021), which can be frequently encountered in calves with diarrhea and azotemia (> 2 mg / dL) due to the increased anaerobic metabolism, primary kidney damage may also occur (SMITH, 2015). Impaired renal function also occurs as a result of the decrease in arterial blood pressure associated with fluid loss, and a deterioration in glomerular filtration rate (BAŞAK et al., 1991; KIYKIM, 2006; PORTILLA and SHAH, 2010). Thus, an increase in creatinine and BUN levels occurs, which are biomarkers of renal functions in calves (BAŞER AND CİVELEK 2013). In the current study, it was found that 65.3% of calves with neonatal diarrhea had azotemia (Creatinine >2 mg/dL). In addition, approximately 34% of the azotemic calves were mild-moderate, while around 32% were severe cases. These results are similar to previous studies (BAŞER and CİVELEK 2013; LEE et al., 2020), and confirm that azotemia is common in calves with diarrhea.

When the conditions causing prerenal azotemia are eliminated, recovery occurs in the majority of cases, but when not corrected, cellular hypoxia, leading to acute tubular necrosis, may develop (KIYKIM, 2006; PORTILLA and SHAH, 2010). For this reason, determining creatinine levels at regular intervals is important for monitoring the development of renal failure and/or determining whether azotemia has improved (MISIRLIOĞLU et al., 2016). In hypovolemias due to fluid loss, early recognition and appropriate treatment of the initial phase is very important, before irreversible renal dysfunction develops. Early symptoms of acute renal failure may go unnoticed by most physicians (BAŞAK et al., 1991). In the present study, it is quite possible that the azotemia observed in the calves was prerenal, but the presence of severe azotemia observed in approximately 32% of the cases suggests that renal dysfunction (possibly acute renal failure) may also have developed. The most important limitation of this study is that the cases were not followed up.

It is known that as the severity of dehydration increases in calves with diarrhea, the danger of azotemia increases (GUZELBEKTES et al., 2007). The results of our study show that blood pH in the severe azotemia group decreased significantly ($P <0.05$) compared to the non-azotemia and mild-moderate azotemia groups, and there was a negative correlation between creatinine level and pH. In addition, although the HCO_3^- and BE values of the severe azotemia group were lower than the other two groups, a statistical difference was only found in the mild-moderate azotemia group. It may be concluded that there is a relationship between the severity of acidemia and azotemia, and it would be beneficial to monitor renal function in calves with acidemia, especially severe cases.

Lactate is a metabolite produced by anaerobic glycolysis. Under normal conditions, low concentrations of lactate are produced in healthy people (FALL and SZERLIP, 2005; HUCKABEE, 1961a; HUCKABEE, 1961b). It has been reported that in calves with diarrhea, the concentration of blood lactate increases, and this occurs as a result of the increase in both L lactate (from anaerobic glucose due to hypovolemia and hypoxia) and D lactate (by bacteria in the intestine) (LORENZ, 2004; OMOLE et al., 2001). AYDOGDU et al. (2019) stated that in calves who did not survive, the blood lactate level was significantly higher than in survivors, and had a prognostic significance. In the present study, as the severity of azotemia increased, a gradual increase in lactate levels was observed, and it was found that the lactate levels in the severe azotemia group were significantly higher ($P <0.05$) compared to the non-azotemia and mild-moderate azotemia groups. Also, there was a positive correlation between creatinine levels and lactate. The most likely cause of this increase in blood lactate level, in parallel with the severity of azotemia, is related to hypovolemia and hypoxia due to dehydration. In our study, $pCO2$ levels were found to be higher in the mild-moderate azotemia and severe azotemia groups compared to the non-azotemia group, and this showed that respiratory acidosis (mean $pCO2> 45$ mm Hg) was also present. In this case, it may be said that calves with azotemia have a greater tendency towards hypoxia.

A common complication observed in calves with diarrhea is hyperkalaemia (COSKUN et al., 2020b). Hyperkalaemia may occur due to a disruption of the Na-K ATPase pump during acidemia, decreased excretion of K^+ from the kidneys, the movement of K^+ from inside the cell to outside the cell, hyponatremia, hypo-osmolality, or cellular hypoxia (CONSTABLE et al., 2018; HARTMANN et al., 1984; NAYLOR et al., 2006; SMITH, 2009). In the present study, it was determined that as the severity of azotemia increased, blood K^+ levels increased. Accordingly, the K^+ levels of the severe azotemia group were found to be significantly higher ($P<0.05$) than in the non-azotemia and mild-moderate azotemia groups. It was also found that there was a positive correlation between creatinine and K^+. TREFZ et al. (2013) stated that azotemia and hyperphosphatemia are risk factors for hyperkalaemia and that hypovolemia, and the accompanying reduction in glomerular filtration rate, strongly indicate that they play a key role in the pathogenesis of hyperkalaemia in such animals. In the present study, it was suggested that this increase in calves with severe azotemia may be due to a decrease in renal K^+ excretion in addition to acidemia.

Ionized calcium is a macro mineral required for many physiological functions in the body, ranging from cellular function, intracellular messenger transduction and hormonal activity, to cardiac function and neuronal activity (HÄSTBACKA and PETTILÄ 2003; TONGPRAYOON et al., 2020a; TONGPRAYOON et al., 2020b; WANG et al., 2019). In human medicine, it has been proven that patients with acute renal failure are often hypocalcemic, with a decrease observed in two of the three main calcium fractions (ionized calcium and total plasma calcium) (BURDMANN and YU, 2001; TONGPRAYOON et al., 2020c). Ionized hypocalcemia is very common in critically ill patients. It was reported to be observed in more than half the critically ill people and is also an important finding in critically ill dogs (LUSCHINI et al. 2011), cats with septic peritonitis (KELLETT-GREGORY et al. 2010), and calves with sepsis (COSKUN et al. 2020a). Similarly, in the current study, it was determined that the level of ionized calcium gradually decreased as the severity of the disease increased. The mechanisms by which critical illness and hypocalcemia are associated are not fully understood, and are presumed to be multifactorial.

In conclusion, it was observed that azotemia is a common occurrence in neonatal calves with diarrhea and that there is a significant relationship between the severity of azotemia and blood gases. Therefore, it may be concluded that it would be beneficial to monitor renal functions during the treatment of calves with neonatal diarrhea.

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Received: 20 May 2021
Accepted: 18 July 2021

AYDOĞDU, U., A. COŞKUN, O. BAŞBUĞ, S. TÜRK, Z. T. AĞAOĞLU: Odnos između težine azotemije i plinova u krvi u 101 teleta s neonatalnom dijarejom. Vet. Arhiv 93, 31-38 2023.

SAŽETAK

Cilj je ovog istraživanja bio procijeniti odnos između težine azotemije i pokazatelja plinova u krvi u 101 teleta s dijarejom. Telad je na temelju razine kreatinina podijeljena u tri skupine: skupina bez azotemije (<2,00 mg/dL), skupina s blagom – umjerenom azotemijom (2,01–5,00 mg/dL) i skupina s teškom azotemijom (>5,01 mg/dL). Azotemija nije otkrivena u 35 od 101 teleta s dijarejom, blaga – umjerena azotemija pronađena je u 34 teleta, a teška azotemija u 32 teleta. Vrijednost pH krvi bila je znakovito niža , a razina kalija i laktata znakovito viša, u skupini s teškom azotemijom u usporedbi s ostalim dvjema skupinama. Iako su vrijednosti HCO_3^- i BE u skupini teladi s teškom azotemijom bile niže nego u drugim skupinama, statistički znakovita je razlika pronađena samo u odnosu na skupinu s blago-umjerenom azotemijom. Razina ioniziranog kalcija (iCa^{+2}) također je bila niža u skupini s teškom azotemijom u usporedbi s drugim skupinama, ali je razlika bila znakovita samo u odnosu na skupinu bez azotemije. Rezultati istraživanja pokazuju da se azotemija često pojavljuje u neonatalne teladi s dijarejom i da postoji znakovita povezanost između težine azotemije i plinova u krvi. Može se stoga zaključiti da bi praćenje bubrežne funkcije bilo korisno u liječenju teladi s neonatalnom dijarejom.

Ključne riječi: azotemija; tele; dijareja; plinovi u krvi