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Original article

Changes in blood acid-base balance parameters and coagulation profile during diarrhea in calves

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Abstract

The purpose of this study was to investigate possible alterations in acid-base balance parameters and the coagulation profile in neonatal diarrheic calves. Twenty neonatal diarrheic and 20 clinically healthy neonatal calves aged between 1 week to 10 days were used. All blood samples were taken on the third day from the onset of diarrhea symptom. Venous blood samples were collected from each animal to determine platelet numbers, pH, pCO₂, pO₂, HCO₃⁻, BE, O₂SAT, ctCO₂ and electrolytes (K⁺, Na⁺ and Cl⁻). Plasma samples were collected from each animal for the measurement of prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), the concentrations of fibrinogen, D-dimer and the activity of antithrombin III (AT III). Blood pH (7.19), BE (-10.6 mmol/l), HCO₃⁻ (25.15 mmol/l), pO₂ (3.33 kPa), O₂SAT (24.12 %) were significantly lower and serum concentration of K⁺ (6.55 mmol/l) was significantly higher in diarrheic calves. These changes indicate the state of uncompensated metabolic acidosis with accompanying hyperkalemia. TT (32.05s) and APTT (39.9s) values were more prolonged in calves with diarrhea than in the control group. D-dimer (587.25 µg/l) concentrations were significantly increased while a visible drop in AT III (103.75%) activity and platelets counts (598 x10⁹/l) were observed in diarrheic group of calves. The results suggest that a consumptive type of disseminated intravascular coagulation (DIC) developed in diarrheic calves.

Key words: calves, neonatal diarrhea, coagulation profile, DIC

Introduction

Neonatal diarrhea is a major cause of economic loss in cattle herds, as a result of retarded growth, cost of treatment, and deaths (Abubakar et al. 2007). The

mortality risk of live-born neonatal calves under 1 month of age has been reported to range from 15% to 30% on farms with serious management problems (Bazeley 2003). The majority of deaths attributable to infectious diseases as diarrhea, pneumonia, and septi-

caemia are the most common disorders. Mortality associated with these diseases appears to result from bacteraemia, viraemia and endotoxemia (Lofstedt et al. 1999). Clinical symptoms observed in calves with diarrhea are manifested by lack of appetite, loose stools and abdominal pain. Longer diarrhea results in dehydration, weakness and loss of sucking reflex. Loss of fluids leads to hypovolaemia and circulation disorders, whereas disturbances in the acid-base balance and electrolytic balance are likely to induce neural symptoms with convulsion leading to death (Grove-White 2004).

It is known that several Gram-negative bacteria containing lipopolysaccharide (LPS), such as *Escherichia coli* and *Salmonella* spp., are important causative agents of diarrhea in calves. Lipopolysaccharides located on cell walls of Gram-negative bacteria play an important role in the development of endotoxemia. (Moore and Morris 1992). Endotoxin is a potent stimulus of the inflammatory response through activation of cytokine-mediated procoagulant effects on endothelial cells (Otto et al. 2000). Endotoxin-induced injury to endothelial cells initiates activation of intrinsic and extrinsic pathways of coagulation through exposure of subendothelial collagen and inducing the release of thromboplastin – tissue plasminogen activator, and plasminogen activator inhibitor (Green and Adams 1992). With overactivation of the haemostatic mechanism, coagulation factors and thrombocytes are excessively consumed, resulting in thrombin formation in the capillary blood vessels. Therefore, ischemia, functional disorders, a tendency for bleeding, and disseminated intravascular coagulation (DIC) may develop in several organs (Levi et al. 1999). DIC is usually associated with several disease states. In broad terms, there are two major pathways that may cause DIC: (i) a systemic inflammatory response which activates the cytokine network and coagulation cascade (such as in severe sepsis and major trauma) and/or (ii) release or exposure of pro-coagulant material into the blood stream (such as in cancer or obstetric patients) (Levi et al. 1997). Disseminated intravascular coagulation is a continuously progressing process, it can be subdivided into three phases: phase I – compensated activation of the haemostatic system, phase II – decompensated activation of the haemostatic system, phase III – full-blown DIC (Bick 1996). The pathologic process is characterized by widespread fibrin deposition in the microcirculation with subsequent ischemic damage, and by the development of a hemorrhagic diathesis caused by the consumption of procoagulans and hyperactivity of fibrinolysis (Morris 1990). In large animals DIC has been described in association with forms of localized and/or systemic septic processes (e.g., salmonellosis, metritis,

mastitis), neoplasia, gastrointestinal disorders (e.g., strangulating intestinal obstruction, acute enteritis, protein-losing enteropathy), renal disease, and hemolytic anemia (Morris 1990).

An analysis of the coagulation profile and its abnormalities is one of the key indicators of systemic homeostasis. In veterinary medicine, changes in the coagulation profile have been reported in dogs after ovariohysterectomy (Sobiech et al. 2011), in cows during indigestion (Gokce et al. 2007), in horses infected with influenza virus (Dąbrowska et al. 2000), in cattle affected with left abomasal displacement (Sobiech et al. 2008) and in newborn calves with respiratory and gastrointestinal tract disease (Gokce et al. 2006, Irmak et al. 2006).

Numerous laboratory tests of haemostasis may be abnormal during DIC; however, no one test consistently or specifically provides a definitive diagnosis (Morris 1990). The minimum laboratory data needed to evaluate haemostasis in large animals are the platelet counts, plasma fibrinogen content, prothrombin time (extrinsic coagulation pathway system), activated partial thromboplastin time (intrinsic coagulation pathway system), fibrin degradation products (including D-dimer), and red blood cell distortion and fragmentation – schistocytes (produced by damage of red blood cells during passage through microvascular thrombi). The results of these tests will also vary according to the severity and fulminant nature of the process and the time of sampling (Morris 1990). D-Dimer assay is one of newer tests for the DIC detection. Plasma levels of D-dimer increase during activation of the fibrinolytic system and plasmin generation (Sandholm et al. 1995, Irmak and Turgut 2005).

The aim of the present study was to investigate the disturbances of acid-base balance indices and advancement of coagulation disorders occurring in the course of diarrhea in neonatal calves.

Materials and Methods

Twenty healthy and 20 neonatal H-F diarrheic calves aged between one week to 10 days were enrolled in the study. Routine clinical examinations were conducted in all calves. Healthy calves did not demonstrate clinically any pathological symptoms, whereas all calves from the experimental group showed predominantly symptoms of diarrhea. All blood samples were taken on the third day from the onset of diarrhea symptom. All experimental procedures followed the principles of animal care and were approved by the Local Ethics Commission for Animal Experiments.

From each animal, 3 ml of peripheral blood was drawn from the jugular vein into a syringe containing 0.1 ml of heparin. These blood samples were immediately analysed on a blood gas analyzer (Siemens Rapid Lab® 248, Siemens Healthcare Diagnostics Inc., Camberely, UK) for pH, partial pressure of carbon dioxide ($p\text{CO}_2$), partial pressure of oxygen ($p\text{O}_2$), concentration of bicarbonate ions (HCO_3^-), excess or deficiency of bases (BE), degree of hemoglobin saturation of oxygen (O_2SAT), total pressure of carbon dioxide (ctCO_2) and electrolytes (K^+ , Na^+ and Cl^-). The assessment of electrolytes levels was carried out with the ion-selective method.

The number of platelets was measured by Siemens ADVIA® 2120i hematology system. Blood samples for coagulation profile examination were collected into plastic test tubes containing 3.2% sodium citrate at a ratio of 1:9. Blood was mixed thoroughly and centrifuged at 2000 rpm for 10 minutes to produce plasma. Changes in the optical density of the following plasma coagulation factors were determined by the chromometric method: the prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT) and the concentrations of fibrinogen. D-dimer level and the activity of antithrombin III were determined with the use of the chromogen substrate method by relying on the colorimetric reaction kinetics at a wave length of 450 nm. The above factors were determined with the use of a Bio-Ksel Coag-Chrom 3003 coagulometer and Bio-Ksel plasma kits.

The results were verified statistically by the Newman-Keul test with the use of Statistica 10.0 software to determine arithmetic means, standard deviations and the significance of differences between means at a confidence level of $p \leq 0.01$.

Results

Over the experimental period, the control calves did not demonstrate clinically any pathological symptoms, whereas all affected calves showed impairment or loss of appetite, depression, roughness, dryness, and decreased elasticity of the skin and predominating symptom diarrhea. All the calves defecated with loose stools yellow or gray-yellow in color, and their internal temperature remained at a level of physiological norms or was slightly lower.

The average pH of blood in diarrheic calves was substantially lower than that in the control group ($p \leq 0.01$), similarly concentration of bicarbonates, partial pressure of oxygen, haemoglobin saturation and base excess parameter (Table 1). Other acid-base balance parameters remained at a similar level in both

groups of calves (Table 1). In case of the parameters of the electrolytic balance, only a significant increase in potassium level was observed in diarrheic calves (Table 1).

After analysis of coagulation parameters, a significant increase ($p \leq 0.01$) in mean TT was observed in affected calves (Table 2). Mean PT was similar in both groups of animals, but APTT was visibly prolonged ($p \leq 0.01$) in calves with symptoms of diarrhea (Table 2). Fibrinogen level was slightly increased in diarrheic calves and D-dimer level increased significantly ($p \leq 0.01$) with a visible drop in AT III ($p \leq 0.01$) activity in these animals. These changes were accompanied by a significant ($p \leq 0.01$) reduction in platelet count (Table 2).

Discussion

The parameters of the acid-base balance in healthy calves remained within physiological norms typical for the species (Grove-White and Michell 2001). In the calves with diarrhea disturbances in the acid-base balance manifested by decreased values of pH, bicarbonate level, partial pressure of oxygen, haemoglobin saturation with oxygen and reduced base reserves were observed. These changes were characteristic for the state of uncompensated metabolic acidosis. The obtained results are similar to those published by Ewaschuk et al. (2004) related to the weekly calves with diarrhea. In the chronic inflammation of the gastrointestinal tract, the loss of bicarbonates and electrolytes (mainly Na and K ions) with faeces is considered as the main cause of such disturbances (Ulutas and Sahal 2005). In the state of the metabolic acidosis, decline in the levels of bicarbonates may result from their binding to hydrogen ions in the extracellular hydrous space (Breen 2001). The status of the acid-base balance is closely linked with the level of electrolytes. Some authors (Bellino et al. 2012) observed a significant decrease in concentrations of chloride and sodium ions in blood of calves with diarrheic symptoms which was connected with their loss with faeces. In our study we did not confirm these findings – level of chloride and sodium ions was similar in all calves. We observed an increase in the level of potassium ion which has a direct relationship with disturbances in the acid-base balance. An increased pH value in serum results in a decreased concentration of potassium ions. In contrast, its decrease leads to an increased concentration of these ions. The mechanism of these interactions consists in the exchange of hydrogen and potassium ions between the extracellular and cellular spaces. This exchange may be evoked by the primary increase in the concentra-

Table 1. Mean values of acid base-balance parameters and electrolyte levels in calf blood ($\bar{x} \pm SD$).

Calves	pH	pCO ₂ kPa	ctCO ₂ mmol/l	HCO ₃ ⁻ mmol/l	pO ₂ kPa	O ₂ SAT %	BE mmol/l	Na ⁺ mmol/l	K ⁺ mmol/l	Cl ⁻ mmol/l
Healthy										
\bar{x}	7.37	9.31	34.15	35.22	5.87	50.11	6.34	139.15	4.56	101.24
SD	0.10	0.45	4.82	2.01	0.97	4.13	0.76	1.23	0.24	1.43
Diarrheic										
\bar{x}	7.19*	8.11	30.11	25.15*	3.51*	24.12*	-10.6*	138.12	6.55*	99.67
SD	0.11	0.37	3.01	1.12	0.43	2.23	2.65	1.11	0.54	2.01

* – denote statistically important at $p \leq 0.01$

Table 2. Mean blood coagulation parameters and platelet count in calves ($\bar{x} \pm SD$).

Calves	TT s	PT s	APTT s	Fibrinogen g/l	D-Dimer μg/l	AT III %	PLT x 10 ⁹ /l
Healthy							
\bar{x}	24.37	27.57	32.95	3.25	286.78	118.87	756.1
SD	2.76	1.34	3.24	0.31	27.67	15.35	19.34
Diarrheic							
\bar{x}	32.05*	26.16	39.9*	4.22	587.25*	103.75*	598.2*
SD	3.52	2.57	5.32	0.78	35.79	10.78	23.51

* – denote statistically important at $p \leq 0.01$

tion of hydrogen ions (pH drop) in the cellular liquid, and results in their shift to cells. In accordance with the rule of electric inertness of systemic fluids, the potassium ions shift in an opposite direction (from a cell to extracellular fluid), thus causing an increase in their plasma concentration (Constable and Grunberg 2013). Metabolic acidosis observed in our study might have developed due to the reported loss of fluid and electrolytes in diarrhea (Bellino et al. 2012). Furthermore, metabolic acidosis accompanying inflammation, sepsis, shock, and hypoxia is known to deteriorate the coagulation profile (Bick 1996). Metabolic acidosis has been thought to trigger DIC, most probably via endothelial sloughing, with the attendant activation of factor XII to XIIa and/or XI to XIa and/or platelet release, and activation of the procoagulant system (Bick 1996).

Significant elongations in TT and APTT values were recorded in diarrheic calves as compared with those in the control group (Table 2). The most common causes of prolonged APTT and TT are reported to be due to the liver failure, vitamin K deficiency, and excessive consumption of clotting factors during the development of DIC (Zbanyszak et al. 2004). Thrombin time is a measure of the rate of fibrinogen to fibrin conversion. It is prolonged when fibrinogen is less than 60 mg/dl, fibrinogen is nonfunctional, or fibrin degradation products (FDPs) are present that interfere with fibrin polymerization. Since hypofib-

rirogenemia is rare in large animals, a prolonged thrombin time most likely would indicate the presence of FDPs (Morris 1990). In most cases, TT is prolonged due to a significant decrease in fibrinogen levels and a substantial increase in levels of fibrin degradation products. TT determination is one of the key laboratory indicators of DIC which is accompanied by significantly prolonged thrombin time (Ten Cate 1999, Wada 2004).

Prothrombin time (PT) is a measure of the extrinsic pathway of prothrombin activation and it is determined by coagulation factors V, VII and X, prothrombin and fibrinogen levels, while it is not affected by the remaining factors and platelet count. In various diseases prolonged PT is most often caused by the degradation of coagulation factors which occur during DIC (Idell 2003). In human medicine, prolonged prothrombin time was observed in various diseases including leukemia, contagious diseases and neoplastic diseases, while the associated DIC is one of the main risk factors of mortality (Gando et al. 1996). We did not observe elongation of PT in calves with diarrhea. These results are in opposite to data obtained by Gokce et al. (2006), who observed significant prolongation of prothrombin time in diarrheic neonatal calves.

Activated partial thromboplastin time test (APTT) is used to evaluate the intrinsic and common pathways. The most common cause of prolonged APTT is increased consumption of clotting factors

during DIC. The liver failure and vitamin K deficiency prolong APTT, since factors II, VII, IX, and X are tested. A disseminated coagulopathy should be manifested by several abnormalities in the coagulation profile, although variable use, synthetic rates, and the half-lives of clotting factors may result in abnormality of only one clotting time (APTT or PT) (Morris 1990). In our study, prolonged APTT was found to be common coagulation profile abnormality in calves suffering from diarrhea in comparison with healthy calves (Table 2) which is indicative for seriously impaired haemostasis which supports the development of DIC. The laboratory diagnosis of DIC is usually based on the prolonged APTT, PT, thrombocytopenia, finding FDPs, schistocytes in blood smears, decreased concentrations of coagulation factors (usually factors V, VIII) and reducing antithrombin III activity (Ralph and Brainard 2012). Excessive coagulation is reflected by reduced plasma concentrations of platelets, coagulant and anticoagulant proteins, and increased concentrations of coagulant by-products. Fibrinolysis is indicated by elevated FDPs or reduced concentrations of fibrinolytic and antifibrinolytic proteins (De Laforcade 2012).

Fibrinogen levels in calves with diarrhea were slightly higher than those found in the control group (Table 2). The increase of fibrinogen concentration might be indicative for increase in production of acute phase reactant proteins and exceeding the production of fibrinogen on its consumption during development of DIC. Research studies investigating the occurrence of DIC in humans have shown that the syndrome is associated with hypofibrinogenemia (Levi 2013). In large animals only during the course of some disorders hypofibrinogenemia is observed (Zbanyszek et al. 2004, Radwińska 2010). It may be the result of the impaired hepatic synthesis, increased consumption during DIC, degradation during primary hyperfibrinolysis, or uncompensated loss during massive hemorrhage. Hypofibrinogenemia is an uncommon manifestation of DIC in large animals and, when present, should strongly suggest the concomitant liver dysfunction (Morris 1990).

D-dimer level increased significantly in calves with diarrhea, while a visible drop in AT III activity and platelet count were observed in this group of animals. D-dimer is a neoantigen formed when thrombin initiates the transition of fibrogen to fibrin and activates factor XIII to crosslink the fibrin formed; this neoantigen is formed as a result of plasmin digestion of crosslinked fibrin (Irmak and Turgut 2005). The D-dimer test is therefore specific for fibrin degradation products (Bick 1996). D-dimer, like thrombin-antithrombin complex (TAT), plasmin-plasmin inhibitor complex (PPIC), soluble fibrin (SF) and ac-

tivated protein C-protein C inhibitor complex (APC-PC), belongs to the most sensitive markers of thrombosis (Minamikawa et al. 1994). These markers have high sensitivity and specificity, but the tests are expensive and the measurements require the use of sophisticated analytical equipment. In the group of the above parameters, D-dimer determination is the only test which has gained widespread popularity and which can be introduced into routine diagnostics. Increased D-dimer plasma concentrations are indicative of secondary activation of the fibrinolysis system, preceded by clotting activation and thrombin production, which are typical DIC symptoms (Matyszczyk et al. 2008). Increased D-dimer levels also suggest that the excessive quantities of fibrinogen converted to fibrin inside blood vessels undergo fibrinolytic degradation. In the vast majority of diseases and clinical conditions, the above is due to procoagulant stimuli which are indicative of acute or chronic thrombotic and embolic changes (Mammen 2000). High levels of D-dimer observed in calves with diarrhea (Table 2) are indicative of seriously impaired haemostasis and the development of secondary fibrinolysis associated with DIC.

Antithrombin III is a measure of the coagulation inhibitor activity. It is recognized as the main thrombin inhibitor and its activity accounts for 50-80% of the plasma antithrombin activity (Pusterla et al. 1997). AT III has an important role in the inflammatory state. It is not only an important physiological inhibitor of coagulation but also possesses anti-inflammatory properties (Mammen 2000). It seems able to promote the endothelial release of prostacyclins, which in turn inhibits leukocyte activation (Okajima and Uchiba 1998). In the present study, AT III activity in calves with diarrhea was significantly lower than that found in the healthy group. There are some reports (Levi et al. 1999) suggesting that decreased anti-proteolytic activity (including a drop in AT III activity) is observed in a state of increased activity and faster consumption of coagulation factors.

Platelet count was considerably lower in calves with diarrhea than in the control group. Many disorders can lead to thrombocytopenia, e.g. reduced or ineffective platelet production, decreased platelet half-life or platelet sequestration. Excessive consumption of platelets to fulfill their normal role in haemostasis occurs during DIC (Morris 1990). Platelet count tests are a useful prognostic tool for monitoring the degree and intensity of consumption and degradation processes in clotting dysfunctions. A study of ruminants has confirmed that thrombocytopenia occurs in diseases which are accompanied by DIC (Gokce et al. 2006, Gokce et al. 2007, Sobiech et al. 2008). It should be noted that a lower thrombocyte count is only one of DIC indicators, and that the diagnostic

value of this parameter is limited and should be analyzed in conjunction with other coagulation factors.

In summary, it may be concluded, that in calves with symptoms of diarrhea there were observed numerous cases of disturbances in systemic homeostasis manifested by incidence of uncompensated metabolic acidosis with accompanied elevation of potassium concentration. Simultaneously with these disorders serious alterations in coagulation profiles including prolongation of TT and APTT, increase in D-dimer level, reduction in AT III activity and decrease in platelet counts were observed. These changes are characteristic for the occurrence of DIC, which may be a serious complication of diarrhea in calves.

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