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Investigation of cytokine levels in calves with naturally occurring sepsis

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ABSTRACT: This study aimed to detect changes in clinical parameters, biochemical and serum cytokine levels in calves with naturally occurring sepsis. In the study, 34 calves diagnosed with sepsis according to clinical and laboratory results and 7 calves deemed to be healthy according to clinical and laboratory results were used. The blood sampling was performed by jugular venapuncture for hematological and biochemical analysis and the determination of cytokine levels. Significant changes were observed in the clinical parameters of calves with sepsis. Serum concentrations of IL-1β, IL-6, IL-10, TNF-α, and INF-γ were significantly increased ($P<0.05$) in calves with sepsis compared to the control group. Also, a significant increase ($P<0.05$) of BUN, creatinine, CK, and CK-MB levels and a significant decrease of TP level ($P<0.05$) were determined in the blood serum of calves with sepsis compared to the control group.

In conclusion, it was concluded that varying degrees of tissue/organ damage developed in calves with sepsis and cytokines played an important role in the development of inflammatory damage during sepsis.

Keywords: Calf; sepsis; cytokine

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INTRODUCTION

Systemic Inflammatory Response Syndrome (SIRS) is a systemic inflammatory response that develops due to infection or non-infectious causes such as trauma, toxins, hyperthermia, burns. Sepsis, defined as a systemic inflammatory response to infections, is an important cause of morbidity and mortality in livestock as well as in humans (Aydogdu et al., 2018; Constable et al., 2018; Coskun et al., 2020). Despite the development of treatment methods applied in intensive care and the use of new drugs that can allow sepsis to be eradicated before it reaches major organs and even becomes fatal, especially in human medicine, sepsis is still a serious condition and mortality rates are above acceptable levels (Novelli et al., 2010; Baykara et al., 2018). Bacteremia and sepsis cases caused by *E. coli* and *Salmonella spp.* are frequently seen in calves. 30% of calves with diarrhoea or no diarrhoea but severe illness are bacteremic and the risk of bacteremia increases with insufficient transfer of colostral immunoglobulins. Low levels of serum protein and immunoglobulins are associated with inadequate transfer of colostral immunoglobulins. This may result in sepsis, mostly caused by gram-negative bacteria, in newborn livestock (Aldridge et al., 1993; Constable et al., 2018). Sepsis can be diagnosed by finding at least 2 SIRS criteria (hyperthermia/hypothermia, bradycardia/tachycardia, tachypnea, leukopenia/leukocytosis) together with a suspected or existing infection (Aydogdu et al., 2018; Aygun and Yildiz, 2018; Yıldız et al., 2018; Coskun et al., 2020).

Cytokines are a group of endogenous inflammatory and immunomodulatory proteins that primarily mediate the pathophysiology of sepsis-associated systemic inflammatory response syndrome. In the sepsis process, both pro and anti-inflammatory cytokines are produced. Pro-inflammatory cytokines (tumor necrosis factor-α, interleukin 1a, interleukin 1b, interleukin 12, interferon γ and interleukin 6) are required to initiate an effective inflammatory process against infection, whereas their overproduction has been associated with multiple organ dysfunction and mortality (Pinsky et al., 1993; Blackwell and Christman, 1996; Schulte et al., 2013). Cytokines are responsible for the activation of macrophages, the development of fibroblasts in inflamed tissue, the activation of leukocyte procurers in the bone marrow, muscle destruction, and from an increase in body temperature (Miert, 1995; Niewold et al., 2003; Tsiotou et al., 2005).

Severe sepsis is sepsis accompanied by organ dysfunction (Constable et al., 2018). Since organ dysfunction also occurs in the advanced stages of sepsis, some important changes can be observed in biochemical parameters related to the organ and the severity of the dysfunction (Basoglu et al., 2014; Aydogdu et al., 2018; Aygun and Yildiz, 2018; Basoglu et al., 2018; Yıldız et al., 2018; Coskun et al., 2020).

This study aimed to determine changes in clinical and biochemical parameters and serum cytokine levels in calves with naturally occurring sepsis.

MATERIAL AND METHODS

Animals

In this study, 34 Holstein breed calves at the age of 2-30 days who were brought to the Selcuk University Faculty of Veterinary Medicine Large Animal Clinic and diagnosed with sepsis as a result of the following criteria and 7 healthy Holstein breed calves at the age of 5-30 days, were used. This study was approved by the ethics committee of Faculty of Veterinary Medicine, Selcuk University.

Clinical Examination and Diagnosis of Sepsis

Calves' body temperature, heart rate, respiratory rate, capillary refill time, degree of dehydration, mucosal examination, mental status and consciousness, standing ability and appetite were evaluated, and recorded.

As a result of clinical examinations, calves with at least two of the criteria (Aydogdu et al., 2018; Aygun and Yildiz, 2018; Yıldız et al., 2018; Coskun et al., 2020) of SIRS (leukopenia/leukocytosis, hypothermia/hyperthermia, tachypnea, bradycardia/tachycardia) together with an existing or suspected infection were diagnosed with sepsis and included in the study. Diarrhoea (n=31), pneumonia (n=2) and omphalitis (n=1) were observed in the calves with sepsis. In calves with diarrhoea, pneumonia in 2 calves, omphalitis in 1 calf, and arthritis in 1 calf were also observed. Calves that met the SIRD criteria but did not have an existing or suspected infection, and calves with a significant infection that did not meet the SIRS criteria were not included in the study.

Taking Blood Samples

For blood analysis, blood was taken from the vena jugularis of healthy and calves with sepsis into anticoagulant-coated tubes (K2EDTA BD Biosciences, San Jose, CA, USA) for haematological examination and serum separation tubes (BD Biosciences, San

Jose, CA, USA) for serum biochemical parameters and cytokines analysis. The blood samples taken for biochemical analysis were kept at room temperature for 15 minutes, and then the sera were separated after centrifugation for 10 minutes at 2500 g. And the serum samples were stored at -80 ° C until analysis.

Hematological and Biochemical Analyzes

Leukocyte count was determined from anticoagulated blood samples via automated blood count device (MS4e, Melet Schloesing Laboratories, France) within 30 minutes. Serum lactate dehydrogenase (LDH), aspartate aminotransferase (AST), total protein (TP), blood urea nitrogen (BUN), creatinine, creatine kinase (CK), and creatine kinase myocardial band (CK-MB) levels in the auto analyzer (BT 3000 plus, Biotecnical Inc, SPA, Rome, Italy) were analyzed. Cardiac troponin I (cTnI, Life Diagnostics, Inc, West Chester, PA, USA), cardiac troponin T (cTnT, Cusabio Biotech Co., Ltd. China), and cytokine levels (TNF-α, IL-1β, IL-6, IL-10, and IFN-γ, Cusabio Biotech Co., Ltd. China) were measured using commercial bovine-specific ELISA kits using a microplate reader (MWGT Lambda Scan 200, Bio-Tek Instruments, Winooski, VT, USA) according to the manufacturer's instructions.

Statistical Analysis

Data were given as mean and standard error of the mean. The statistical difference between the two groups was analyzed by independent t test. The level of statistical significance was accepted as $P<0.05$. A statistical software program (SPSS 15.0) was used for statistical analysis.

RESULTS

Tachycardia or bradycardia and tachypnea were detected in calves with sepsis. While the body temperature of calves varied between 35°C and 42°C, prolonged of capillary refill time was found in almost all of them (Table 1). Severe dehydration (10%) was observed in some of the calves with sepsis, while some did not. The mucous membranes of the sick calves had varying degrees of symptoms (anemic, hyperemic, and dirty hyperemic). The sucking reflex was absent or very weak in the calves with sepsis. While some of the calves with sepsis had complete loss of consciousness, some of them were conscious. When the ability to stand was observed, findings ranging from lateral recumbency to weakness were observed.

Leucopenia was observed in 4 of the calves with sepsis, leukocytosis was observed in 21, and leukocyte levels were within the reference limits (4-12 10^3/mm^3) in 9 of them.

Table 1. Changes in clinical findings of calves with healthy and sepsis (Mean ± SEM)

Parameters	Sepsis (n=34)	Control (n=7)	P
Temperature (°C)	37.97±0.31	38.88±0.07	0.070
Heart rate (min)	116.06±5.08	99.28±4.10	0.160
Respiratory rate (min)	43.28±4.70	24.14±1.16	<0.001
CRT (sec)	4.44±0.21	1.71±0.18	<0.001

CRT: Capillary refill time

Table 2. Changes of biochemical parameters in calves with healthy and sepsis (Mean ± SEM)

Parameters	Sepsis (n=34)	Control (n=7)	P
BUN (mg/dL)	44.56±5.19	23.14±2.32	**0.001**
Creatinine (mg/dL)	2.30±0.29	0.93±0.04	**<0.001**
TP (g/dL)	5.15±0.28	6.80±0.19	**<0.001**
AST (U/L)	127.41±13.99	81.14±18.90	0.070
LDH (U/L)	902.66±64.12	848.57±54.75	0.527
CK (U/L)	708.56±133.84	53.71±10.62	**<0.001**
CK-MB (U/L)	250.06±37.33	60.29±12.48	**<0.001**
cTnI (ng/mL)	0.42±0.30	0.06±0.02	0.240
cTnT (ng/mL)	0.22±0.12	0.11±0.01	0.170

BUN: blood urea nitrogen, TP: total protein, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase, CK-MB: creatine kinase myocardial band, cTnI: cardiac troponin I, cTnT: cardiac troponin T

Table 3. Serum IL-1β, IL-6, IL-10, TNF-α and INF-γ levels of calves with healthy and sepsis (Mean ± SEM)

Parameters	Sepsis (n=34)	Control (n=7)	P
IL-1β (pg/mL)	16.93±3.23	4.11±0.92	0.001
IL-6 (pg/mL)	18.55±2.90	7.61±0.67	0.001
IL-10 (pg/mL)	30.93±9.47	6.63±0.51	0.015
TNF-α (pg/mL)	292.51±88.44	64.33±2.16	0.015
IFN-γ (pg/mL)	1423.25±254.16	827.84±57.68	0.028

IL-1β: interleukin 1 beta, IL-6: interleukin 6, IL-10: interleukin 10, TNF-α: tumour necrosis factor alpha, IFN-γ: interferon gamma

The changes in biochemical parameters of calves with sepsis and healthy are given in Table 2. When compared with the control group, serum BUN, creatinine, CK and CK-MB levels increased significantly ($P<0.05$), and TP level decreased significantly ($P<0.05$) in calves with sepsis.

Changes in serum cytokine levels of calves with sepsis and healthy are given in Table 3. Serum IL-1β, IL-6, IL-10, TNF-α, and INF-γ concentrations were significantly increased ($P<0.05$) in calves with sepsis compared to the control group.

DISCUSSION

Sepsis is a complex condition that develops as a systemic response of the body to infection and can lead to multiple organ dysfunction and death (Bodur et al., 2006). Multiple organ dysfunction may be encountered during the course of sepsis. Sepsis has negative effects on renal functions. Aydogdu et al. (2018) found that BUN and creatinine levels increased significantly in calves with sepsis compared to healthy ones. It has been stated that high serum urea nitrogen concentration is observed in acute endotoxemia and this increase is a reflection of the decrease in glomerular filtration (Constable et al., 2018). The azotemia (increase in BUN and creatinine concentrations) observed in calves with sepsis in the study may be associated with a decrease in glomerular filtration. In acute endotoxemia, there is a low serum total protein concentration. The decrease in total protein concentration may be associated with increased capillary permeability. In addition, low levels of serum protein and immunoglobulins are also associated with inadequate transfer of colostral immunoglobulins. This condition, which is called failure of passive transfer, may result in sepsis mostly caused by gram-negative bacteria in newborn livestock (Constable et al., 2018). Başoğlu et al. (2004) have been reported that calves with septicemia had failure of passive transfer. Aydoğdu et al. (2019) have been reported that low TP level in calves with diarrhoea may be an indicator of failure of passive transfer. Aydogdu and Guzelbektes (2018) also stated that the TP levels of calves with failure of passive transfer are low. In this study, TP level of calves with sepsis was found significantly lower ($P<0.05$) compared to the control group. This decrease in total protein level may have developed due to increased capillary permeability and failure of passive transfer. In addition, the increase in enzyme levels such as AST and CK showed varying degrees of tissue/organ damage in calves with sepsis.

Cardiac dysfunction develops due to sepsis and it is stated that this is associated with increased inflammation, impaired energy metabolism (suppression of fatty acid and glucose oxidation and associated ATP depletion) and weakened adrenergic signal in the heart. This cardiac dysfunction due to sepsis affects mortality significantly (Drosatos et al., 2015). Naseri et al. (2019) reported that circulatory dysfunction is more prevalent than systolic dysfunction in septic calves. Cardiac specific biomarkers such as CK-MB, cTnI and cTnT are used to detect myocardial cell damage in cattle and calves (Karapınar et al., 2010; Aydogdu et al., 2016). In a study, significant increases in cTn-I level were found in calves with experimental endotoxemia (Peek et al., 2008). Kirbas et al. (2021) determined that sepsis may cause myocardial damage in neonatal calves. In this study, cTnI and cTnT concentrations were determined as 0.42 ± 0.30 and 0.22 ± 0.12 ng/ml, respectively. Although troponin levels were high in the group with sepsis, no statistical difference was observed between the groups, but a significant ($p<0.05$) difference was found in serum CK-MB values. It was evaluated that myocardial damage might have developed in calves with sepsis due to the increase in the levels of CK-MB, cTn-I and cTn-T parameters.

Production of both pro and anti-inflammatory cytokines is formed due to systemic inflammatory response syndrome associated with sepsis (Schulte et al., 2013). Pro-inflammatory cytokines are mostly produced by activated macrophages. It has been reported that some pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α are involved in the pathological pain process (Zhang and An, 2007) and have important effects on the pathogenesis of inflammation (El-Ashker et al., 2012; Galvao et al., 2012; El-Deeb and Tharwat, 2014). INF-gamma is a specific activator of macrophage functions and has a critical role in the host immune response in bacterial infections (Qiu et al., 2001). Interleukin-1 is one of the cytokines that play an important role in acute and chronic inflammation. IL-1 family includes cytokines IL-1α, IL-1β, IL-1 receptor antagonist (IL-1RA), IL-1F5-10 and IL-33. IL-1β is one of the powerful pro-inflammatory cytokines and has many functions including cell survival and proliferation (Börekci et al., 2014). IL-6 is a pleotropic cytokine that causes a variety of biological activities in different target cells. It regulates immune response, hematopoiesis, acute phase response and bone metabolism. IL-6 has been shown to stimulate acute phase proteins and antibody production by stimulating B cells and hepatocytes. It has been observed that IL-6 prolongs the life span of neutrophils coming to the inflammation zone and thus the inflammation response (Okajima, 2001; Van Gucht et al., 2004). High IL-6 levels have been determined in 64-100% of patients with septic shock (Riche et al., 2000; Cavaillon and Conquy, 2002). TNF-α is one of the important cytokines in the early stages of sepsis formation and pathophysiology (Tsiotou et al., 2005). Serum TNF-α level in healthy individuals is usually undetectable. However, in the process of sepsis and critical diseases, it increases with endogenous and exogenous stimulating factors (bacteria, virus, tumor, cell damage) (Worthley, 2000). Başoğlu et al. (2004) stated that the TNF-α concentration in calves with septicemia was related to the clinical condition of the calves. Albayrak and Kabu (2016) reported that a significant increase in pro-inflammatory cytokine levels (TNF-α, IL-1β and IL-6) was observed in calves with diarrhoea. In this study, TNF-α, IL-1β, IL-6 and IFN-γ concentrations were found to be significantly higher ($P<0.05$) in calves with sepsis compared to healthy calves, and it was evaluated that pro-inflammatory cytokines had significant effects on the pathogenesis of sepsis inflammation. Anti-inflammatory cytokines are a set of immunoregulatory molecules that control the pro-inflammatory cytokine response. Among all anti-inflammatory cytokines, IL-10 is a cytokine with potent anti-inflammatory properties by suppressing the expression of inflammatory cytokines such as TNF-α, IL-6 and IL-1 by active macrophages (Zhang and An, 2007). IL-10 has been shown to play a major role in balancing the pro-inflammatory response in various infectious diseases (Gelderblom et al., 2007; Sharma et al., 2011; Yilma et al., 2012). In the presented study, IL-10 concentration was found significantly higher ($P<0.05$) in calves with sepsis compared to healthy calves. This increase in IL-10 concentration was probably related to the control of the pro-inflammatory cytokine response in sepsis.

In conclusion, the observation of abnormalities in clinical and biochemical parameters in calves with sepsis showed varying degrees of tissue/organ damage and it was concluded that pro-inflammatory and also anti-inflammatory cytokines play an important role in the development of inflammatory damage during sepsis.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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