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*Original article*

# The evaluation of hemostatic dysfunction and disseminated intravascular coagulation in dairy cows with abomasal displacement

M. Maden<sup>1</sup>, R. Yildiz<sup>2</sup>, R. Çöl<sup>3</sup>, M. Arican<sup>4</sup>, M. Ider<sup>1</sup>, M. Garip<sup>5</sup>, B. Tras<sup>6</sup>

<sup>1</sup> Department of Internal Medicine, Faculty of Veterinary Medicine, Selcuk University, 42003, Konya, Turkey

<sup>2</sup> Department of Internal Medicine, Faculty of Veterinary Medicine, Mehmet Akif University, 15030, Burdur, Turkey

<sup>3</sup> Department of Physiology, Faculty of Veterinary Medicine, Selcuk University, 42003, Konya, Turkey

<sup>4</sup> Department of Surgery, Faculty of Veterinary Medicine, Selcuk University, 42003, Konya, Turkey

<sup>5</sup> Department of Animal Breeding, Faculty of Veterinary Medicine, Selcuk University, 42003, Konya, Turkey

<sup>6</sup> Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Selcuk University, 42003, Konya, Turkey

## Abstract

Disseminated intravascular coagulation (DIC) is a complex, dynamic and hemostatic disorder which develops secondarily to a disease characterized with an imbalance in the pro-coagulant and anti-coagulant components of hemostasis. The aim of the study is to evaluate hemostatic dysfunction and the DIC syndrome in cattle with displaced abomasum (DA), with using the hematologic analyses and an extensive coagulation profile in the 96 hour-period including before and after surgery. The animal material of the study consisted of 12 dairy cows diagnosed with displaced abomasum (9 LDA and 3 RDA without volvulus) in the 2-4 week period after parturition and with no other post-partum disease. In dairy cows diagnosed with DA, hematological, coagulometric (PT, APTT, Fibrinogen) and coagulation factor analyses [D-Dimer, TAT (thrombin-anti-thrombin complex), ATIII (antithrombin III), PAI-1 (plazminogen activator inhibitor-1)] were performed in blood samples obtained before the operation as well as 30 minutes, 60 minutes and 2, 5, 10, 24, 48, 72 and 96 hours after the operation. In the DA cases, abnormalities were found in 6 of the 8 coagulation parameters. In the LDA and RDA groups, prolonged PT (sec), PT (INR) and APTT, hypofibrinogenemia, an increase in serum D-Dimer concentration at 72 and 96 hours after the operation and an increase in serum ATIII concentrations before and 30, 60 minutes and 2, 5, 72 and 96 hours after the operation was found ( $p < 0.05$ ). Hemostatic dysfunction and the risk of DIC developing in DA cases and continuing in the post-operative period was determined.

**Key words:** DIC, hemostatic dysfunction, LDA, RDA, dairy cow

## Introduction

Displaced abomasum (DA) is an economically significant and multifactorial disease commonly seen in high-yielding dairy cows during the 3-4 week post-partum period. A large proportion of DA cases occurs on the left side (left displaced abomasum, LDA), while displacement to the right side (right displaced abomasum, RDA) and abomasal volvulus is seen less frequently (Constable et al. 1992, Geishauser 1995).

Disseminated intravascular coagulation (DIC) is a complex disorder with variable pathophysiology which depends a great deal on triggering events, host response and co-morbid conditions. As a result of these complicated interactions, the clinical picture and laboratory findings are variable and this influences diagnosis and treatment approaches (Bick 1994). DIC is assessed with combinations of hemostatic test results. In general, it is reported to be determined by intermediate thrombocytopenia, prolonged PT, low fibrinogen and increasing fibrinolytic products (FDP, D-Dimer) (Stokol 2012). In veterinary practice, DIC is diagnosed according to clinical and laboratory criteria. Alongside clinical criteria, the presence of two or more abnormal laboratory findings is essential (Ritt et al. 1997). It is stated that a diagnosis of DIC may be made by determining three components from the following profile: prolonged APTT (Activated Partial Thromboplastin Time) and PT (Prothrombin Time), presence of FDP, low fibrinogen (FIB) concentration and thrombocytopenia (Estrin et al. 2006). A limited number of studies on DIC are available in DA cases and they contain different statements. It has been reported that hemostatic dysfunction and DIC may develop as a result of defects in the abomasal mucosa in DA cases (Maden et al. 2012); that there is no difference in APTT and PT values before and after the operation in LDA cases (Ogurtan et al. 2003); that prolonged TT (Thromboplastin Time), PT and APTT, an increase in FIB and D-Dimer, a decrease in ATIII and PLT (platelet) levels (Sobiech et al. 2008) and prolonged APTT ( $\geq 58.1$  sec) were encountered (Karakurum et al. 2009) and that abnormal coagulation profiles (prolonged APTT, FDPs increase and thrombocytopenia) were identified in 2 out of 10 animals with LDA and in 3 out of 10 animals with RDA (Irmak and Turgut 2005). In this concept, there are still topics relating to hemostatic dysfunction and DIC diagnosis in cases of DA that need investigating.

The purpose of this study is to evaluate hemostatic dysfunction and the DIC syndrome using hematologic analyses and a wide coagulation profile [(PT, APTT, Fibrinogen, D-Dimer, TAT (thrombin-antithrombin complex), ATIII (antithrombin III), PAI-1 (plazmino-

gen activator inhibitor-1), RBC and PLT indices] in the 96-hour period before and after the operation in dairy cows with displaced abomasum.

## Materials and Methods

### Animals

The animal material of the study consisted of 12 Holstein Friesian dairy cows (3–6 years old) diagnosed with displaced abomasum (9 LDA and 3 RDA without volvulus) in the 2-4 week period (14-30 DIM) after parturition and with no other post-partum disease. The animals with displaced abomasum were admitted to clinic from small family dairy farms or middle size dairy farms. These farms had different feeding management.

For the control group, 12 healthy dairy cows in the 2-4 week post-partum period (14-30 DIM) receiving the same husbandry and nutrition were used. The number of cows with RDA (n=3) admitted to our clinic has been limited. This condition is related with the delayed diagnosis of RDA cases with more severe gastrointestinal disorders and clinical symptoms such as dehydration and acid base balance in the field conditions. All animals diagnosed with displaced abomasum were examined for post-partum diseases (mastitis, metritis, retentio secundinarium, pneumonia, hoof problems, ketosis etc.). Animals suffering from a different disease other than DA were not included in the study. This study has been approved by the Selçuk University Veterinary Faculty Local Ethics Committee (2011/15).

### Diagnosis of Abomasal Displacement

DA diagnosis in the dairy cows was made based on routine physical examination, laboratory tests (hematological tests and blood gases) and specific DA tests (ping on auscultation and percussion, fluid splashing, liptak test, ultrasonography and lost liver percussion area in RDA). In the ultrasonographic examination, DC-6 Vet Diagnostic Imaging System (Shenzhen Mindray, China) equipped with a real-time 3.5-5.0-MHz convex transducer probe used. Cases clinically diagnosed with DA were operated at the Veterinary Faculty Surgery Clinic.

### DA Operation Method

DA surgery was performed via a right flank approach. Following examination of the abdominal cavity, in LDA cases, the abomasum was punctured and the gas and fluid contents emptied; after which, the fixing (omentopexy) procedure was performed by

placing three horizontal U sutures using No. 3 silk suture material starting from the greater omentum majus section of the abomasum to 2 cm caudal of the right flank incision line. In RDA cases, following routine laparotomy, contents of the abomasum were aspirated and a toggle pin was placed within the abomasum through the aspiration hole. After placement of the toggle pin, the aspiration hole was closed routinely and the abomasum returned to its normal position. The free ends of the toggle pin were then fixed to the abdominal wall to a position the size of the palm of a hand behind the sternum and the same distance to the right of the ventral line (abomasopexy).

### Laboratory Analysis

Blood samples were collected from the jugular vein from the dairy cows diagnosed with DA before the operation, as well as 30 and 60 minutes, and 2, 5, 10, 24, 48, 72 and 96 hours after the operation. Blood samples with an anticoagulant (EDTA) were used for hematological analysis (complete blood count) and citrated blood samples were used for coagulometric analysis (prothrombin time/PT, activated partial thromboplastin time/APTT, fibrinogen/FIB); blood samples without an anticoagulant were used for the analysis of coagulation factors (D-Dimer, Antithrombin III/ATIII, Thrombin-antithrombin complex/TAT, Plasminogen activator inhibitor-1/PAI-1).

### Determination of PT

For this purpose, 25  $\mu\text{L}$  citrated plasma (1/9 v/v) was incubated at 37°C for 1 minute in a digital coagulometer (DIAchrom, Dialab), and 50  $\mu\text{L}$  thromboplastin liquid reagent (calcium thromboplastin obtained from rabbit brain, PACIFIC ASSAY) heated at 37°C for 5 minutes was added for coagulation to commence. At the formation of the first coagulation, PT was measured in seconds by the digital timer of the coagulometer.

### Determination of APTT

25  $\mu\text{L}$  citrated plasma and 25  $\mu\text{L}$  APTT EA liquid kit (phospholipid cephaloplastin reagent obtained from rabbit brain, Dialab, C 01130, Austria) was incubated in a digital coagulometer (DIAchrom, Dialab) at 37°C for 5 minutes and 25  $\mu\text{L}$   $\text{CaCl}_2$  solution (0.020 mol/L, sodium azide 0.95 gr/L, 37°C) was added to this combination, starting coagulation. With the formation of the first clot, APTT was measured in seconds by the digital timer of the coagulometer.

### Determination of FIB level

10  $\mu\text{L}$  citrated plasma and 90  $\mu\text{L}$  imidazole buffer was incubated in a digital coagulometer (DIAchrom, Dialab) at 37°C for 60 second and 25  $\mu\text{L}$  fibrinogen reagent (Cattle thrombin, Dialab, Austria) was added to this combination and coagulation initiated. The fibrinogen amount was recorded in grams when the digital timer of the coagulometer stopped.

### Determination of serum ATIII, D-Dimer, TAT, PAI-1 levels

This was performed using the ELISA method (ELX 800 General microplate reader, ELX50 General microplate washer, BIOTEK, USA; printer, KxP1150 panasonic, JAPAN). Samples were processed in microplates using cattle specific ELISA kits (Shanghai Sunred Biological Technology Co., Ltd, Shanghai, China) according to the manufacturer's instructions. Results were recorded at 450 nm wavelength in the microplate reader. From the readings obtained, standard concentrations versus standard absorbance was illustrated on a graph. ATIII, D-Dimer, TAT and PAI-1 concentrations were calculated for unknown samples and controls using the standard curve.

### Statistical Analysis

Data analysis was performed using the IBM SPSS 21.0 software package and the  $p < 0.05$  value was considered to be significant. Using the software package, the Shapiro-Wilk test was applied to determine whether the data exhibited normal distribution. The variance analysis using the Kruskal Wallis test was determined, while the Mann Whitney U test was used for multiple comparisons. In tables, Median, Max and Min values were used.

### Results

A statistically significant increase was found in the serum D-Dimer concentrations of the experimental groups compared to the control group, 72 and 96 hours after the operation. While no difference was seen in the serum ATIII concentration between the control and LDA groups, a significant increase ( $p < 0.05$ ) was observed in the RDA group compared to the control group, before the operation and 30 minutes, 60 minutes, 2, 5, 72 and 96 hours after the operation. Only in the LDA group, a significant decrease was determined in the serum TAT concentration at 24 hours, compared to before the operation. No difference was seen either between or within groups with respect to serum PAI-1 concentration (Table 1).

Table 1. Coagulation factors in control, LDA, and RDA groups.

Parameters	Groups	Sampling time, Median, (minimum-maximum values)										
		Before operation	After operation	30 <sup>th</sup> minutes	60 <sup>th</sup> minutes	2 <sup>nd</sup> hours	5 <sup>th</sup> hours	10 <sup>th</sup> hours	24 <sup>th</sup> hours	48 <sup>th</sup> hours	72 <sup>nd</sup> hours	96 <sup>th</sup> hours
D-Dimer ng/ml	C	731 (419-1061)	731 (419-1061)	731 (419-1061)	731 (419-1061)	731 (419-1061)	731 (419-1061)	731 (419-1061)	731 (419-1061)	731 (419-1061)	731 <sup>B</sup> (419-1061)	731 <sup>B</sup> (419-1061)
	LDA	687 (388-1814)	576 (359-2230)	534 (431-2900)	661 (433-1861)	591 (277-3371)	560 (478-2028)	763 (447-2195)	681 (437-1424)	1177 (548-1834)	1386 <sup>AB</sup> (512-2876)	1751 <sup>A</sup> (648-2819)
	RDA	955 (621-1544)	947 (638-1831)	719 (554-1855)	695 (367-2295)	765 (486-2056)	1317 (437-1423)	1138 (499-1795)	1360 (412-1547)	826 (609-1491)	2631 <sup>A</sup> (716-2962)	2007 <sup>A</sup> (851-2572)
TAT ng/ml	C	19 (11-41)	19 (11-41)	19 (11-41)	19 (11-41)	19 (11-41)	19 (11-41)	19 (11-41)	19 (11-41)	19 (11-41)	19 (11-41)	19 (11-41)
	LDA	30 <sup>a</sup> (10-87)	17 <sup>ab</sup> (12-54)	19 <sup>ab</sup> (8-53)	19,3 <sup>ab</sup> (12-64)	22 <sup>ab</sup> (15-57)	14 <sup>ab</sup> (10-44)	15 <sup>ab</sup> (11-47)	15 <sup>b</sup> (13-31)	14 <sup>ab</sup> (11-39)	11 <sup>ab</sup> (6-37)	20 <sup>ab</sup> (10-37)
	RDA	36 <sup>ab</sup> (12-105)	23 <sup>ab</sup> (16-56)	90,6 <sup>a</sup> (20-95)	32 <sup>ab</sup> (13-62)	29 <sup>ab</sup> (16-73)	19 <sup>ab</sup> (12-50)	15 <sup>b</sup> (12-20)	28 <sup>ab</sup> (13-45)	28 <sup>ab</sup> (13-30)	25 <sup>ab</sup> (8-35)	39 <sup>ab</sup> (11-43)
ATIII mg/dl	C	149 <sup>B</sup> (24-331)	149 (24-331)	149 <sup>B</sup> (24-331)	149 <sup>B</sup> (24-331)	149 <sup>B</sup> (24-331)	149 <sup>B</sup> (24-331)	149 (24-331)	149 (24-331)	149 (24-331)	149 <sup>B</sup> (24-331)	149 <sup>B</sup> (24-331)
	LDA	319 <sup>ABab</sup> (150-1067)	189 <sup>ab</sup> (75-617)	291 <sup>ABab</sup> (166-1020)	244 <sup>ABab</sup> (194-719)	272 <sup>ABab</sup> (225-581)	252 <sup>ABab</sup> (188-1634)	272 <sup>a</sup> (210-3484)	173 <sup>b</sup> (116-491)	189 <sup>ab</sup> (95-506)	533,4 <sup>ABab</sup> (132-613)	486 <sup>ABab</sup> (135-610)
	RDA	455 <sup>A</sup> (218-487)	326 (146-427)	562 <sup>A</sup> (239-578)	284 <sup>A</sup> (222-504)	500 <sup>A</sup> (247-519)	575 <sup>A</sup> (260-889)	3350 (542-6158)	268 (86-515)	270 (112-450)	562 <sup>A</sup> (449-719)	536 <sup>A</sup> (492-562)
PAI-1 ng/ml	C	21 (8-30)	21 (8-30)	21 (8-30)	21 (8-30)	21 (8-30)	21 (8-30)	21 (8-30)	21 (8-30)	21 (8-30)	21 (8-30)	21 (8-30)
	LDA	52 <sup>ab</sup> (10-159)	51 <sup>ab</sup> (20-81)	30 <sup>a</sup> (18-118)	38 <sup>ab</sup> (22-87)	41 <sup>ab</sup> (18-93)	28 <sup>ab</sup> (17-40)	28,2 <sup>b</sup> (15-35)	35 <sup>ab</sup> (17-71)	37 <sup>ab</sup> (12-83)	27 <sup>ab</sup> (13-89)	26 <sup>ab</sup> (18-87)
	RDA	84 (18-91)	89 (51-102)	32 (22-47)	51 (22-85)	81 (42105)	34 (23-79)	33 (22-36)	56 (12-77)	56 (23-87)	39 (23-90)	37 (16-85)

A, B, C and a, b, c; Different letters in the same rows and columns are statistically significant (Kruskall wallis,  $p < 0.05$ ). C, control, healthy animals; LDA, left displaced abomasum; RDA, right displaced abomasum; D-Dimer, TAT (thrombin-antithrombin complex), ATIII (antithrombin III), PAI-1 (plazminogen activator inhibitor-1).

A significant increase ( $p < 0.05$ ) was determined in plasma PT (sec) levels at every measurement time except 2 hours after the operation; also a significant increase ( $p < 0.05$ ) was found in plasma PT (INR) levels between the control groups and experimental groups at every measurement. In the comparison of plasma PT values (sec) between the LDA and RDA groups, a drop at 30 minutes after the operation and a rise at 5 hours after the operation were determined in the RDA group ( $p < 0.05$ ). With respect to plasma PT (INR), a significant increase ( $p < 0.05$ ) 5 hours after the operation was detected in the RDA group, compared to the LDA group. A significant decrease ( $p < 0.05$ ) in the plasma PT (INR) levels was determined 2 hours after the operation in both the LDA and RDA groups (Table 2).

Between the control group and experimental groups, it was observed that serum APTT (sec) displayed a significant increase ( $p < 0.05$ ) at all measurement times except 30 minutes and 2, 48 and 72 hours after the operation. However, in the comparison between the LDA and RDA groups, serum APTT was determined to be significantly higher ( $p < 0.05$ ) in the

RDA group, 5, 10 and 24 hours after the operation. In evaluations within the group, a significant decrease ( $p < 0.05$ ) at 30 minutes and 2 and 5 hours after the operation in the LDA group; a significant decrease ( $p < 0.05$ ) at 30 minutes and 48 hours after the operation and a significant increase ( $p < 0.05$ ) at 10 and 24 hours after the operation in the RDA group was observed (Table 2).

As regards the plasma FIB concentration, there was a significant decrease ( $p < 0.05$ ) at all measurement times, except 2, 10, 24 and 48 hours after the operation between the control and LDA group. However, in the RDA group, a significant decrease ( $p < 0.05$ ) before, after and 96 hours after the operation was determined. Between the LDA and RDA groups, compared to the LDA group and in the RDA group FIB concentration was seen to be higher at 60 minutes after the operation only. No significant difference was observed in the evaluation within the group (Table 2).

In comparison to the control group, a significant increase ( $p < 0.05$ ) was determined in PLT and PCT concentrations after the operation in the experimental

Table 2. Clotting times and coagulation factors in control, LDA, and RDA groups.

Pa- ra-me- ters	Groups	Sampling time, Median, (minimum-maximum values)										
		Before operation	After operation	30 <sup>th</sup> minutes	60 <sup>th</sup> minutes	2 <sup>nd</sup> hours	5 <sup>th</sup> hours	10 <sup>th</sup> hours	24 <sup>th</sup> hours	48 <sup>th</sup> hours	72 <sup>nd</sup> hours	96 <sup>th</sup> hours
PT sec	C	30 <sup>B</sup> (25,3-38,6)	30 <sup>B</sup> (25,3-38,6)	30 <sup>C</sup> (25,3-38,6)	30 <sup>B</sup> (25,3-38,6)	30 (25,3-38,6)	30 <sup>C</sup> (25,3-38,6)	30 <sup>B</sup> (25,3-38,6)	30 <sup>B</sup> (25,3-38,6)	30 <sup>B</sup> (25,3-38,6)	30 <sup>B</sup> (25,3-38,6)	30 <sup>B</sup> (25,3-38,6)
	LDA	85,1 <sup>Aa</sup> (28,9-116,5)	87,6 <sup>Aa</sup> (62,1-96,5)	78 <sup>Aa</sup> (29,3-87,2)	81,4 <sup>Aa</sup> (24,4-93)	34,4 <sup>b</sup> (22,3-82,4)	72 <sup>Bab</sup> (32,1-85,6)	88,4 <sup>Aa</sup> (31,0-112,2)	66,8 <sup>Aab</sup> (28,7-90,6)	68,3 <sup>Aab</sup> (33,6-77,8)	73,6 <sup>Aab</sup> (35,8-86,5)	74,6 <sup>Aa</sup> (38,3-89,3)
	RDA	85,3 <sup>Aa</sup> (84,6-89,7)	84,6 <sup>Aa</sup> (77,6-92,4)	63,6 <sup>Bab</sup> (54,7-67,3)	78,3 <sup>Aa</sup> (77,4-95,5)	45,4 <sup>b</sup> (22,9-51)	90,8 <sup>Aa</sup> (81,4-92)	92,1 <sup>Aab</sup> (92,1-92,1)	67,9 <sup>Aab</sup> (61,4-93,5)	73,4 <sup>Aab</sup> (68,5-76,7)	61,1 <sup>Aab</sup> (37,6-67,8)	69,7 <sup>Aab</sup> (65,5-71,2)
PT INR	C	2,675 <sup>B</sup> (2,2-3,4)	2,675 <sup>B</sup> (2,2-3,4)	2,675 <sup>B</sup> (2,2-3,4)	2,675 <sup>B</sup> (2,2-3,4)	2,675 (2,2-3,4)	2,675 <sup>C</sup> (2,2-3,4)	2,675 <sup>B</sup> (2,2-3,4)	2,675 <sup>B</sup> (2,2-3,4)	2,675 <sup>B</sup> (2,2-3,4)	2,675 <sup>B</sup> (2,2-3,4)	2,675 <sup>B</sup> (2,2-3,4)
	LDA	7,81 <sup>Aab</sup> (2,5-10,6)	7,89 <sup>Aa</sup> (5,6-8,9)	6,91 <sup>Aab</sup> (2,6-7,6)	7,22 <sup>Aab</sup> (2,1-8,3)	3,0 <sup>c</sup> (2,0-7,3)	6,17 <sup>Bbc</sup> (2,8-7,6)	7,89 <sup>Aab</sup> (2,7-10,9)	5,89 <sup>Abc</sup> (2,5-8,0)	6,05 <sup>Abc</sup> (3,6-9)	6,72 <sup>Aabc</sup> (3,2-7,7)	6,33 <sup>Aab</sup> (3,4-7,9)
	RDA	7,57 <sup>Aa</sup> (7,6-7,7)	7,51 <sup>Aa</sup> (7,2-8,2)	5,92 <sup>Aab</sup> (4,8-6,0)	6,94 <sup>Aa</sup> (6,9-8,5)	4,0 <sup>b</sup> (2,0-4,5)	8,06 <sup>Aa</sup> (7,2-8,2)	8,205 <sup>Aab</sup> (8,2-8,2)	6,01 <sup>Aab</sup> (5,4-8,1)	6,5 <sup>Aab</sup> (6,1-6,8)	5,4 <sup>Aab</sup> (3,3-6,0)	6,01 <sup>Aab</sup> (5,8-6,4)
APTT sec	C	40 <sup>B</sup> (29,9-47)	40 <sup>B</sup> (29-47)	40 (29-47)	40 <sup>B</sup> (29-47)	40 (29-47)	40 <sup>B</sup> (29-47)	40,6 <sup>C</sup> (29,9-47,4)	40,6 <sup>C</sup> (29,9-47,4)	40,6 (29,9-47,4)	40,6 (29,9-47,4)	40,6 <sup>B</sup> (29,9-47,4)
	LDA	61,5 <sup>Aab</sup> (42,9-84,6)	72,5 <sup>Aa</sup> (53,6-84,7)	39,5 <sup>d</sup> (30,2-48,1)	52 <sup>Abcd</sup> (36,1-78,1)	41 <sup>cd</sup> (33,5-63)	40,7 <sup>Bcd</sup> (27-84)	53,1 <sup>Babc</sup> (46,0-84,2)	58,7 <sup>Babc</sup> (23,4-86,7)	44,7 <sup>bcd</sup> (34,0-103,8)	44 <sup>bcd</sup> (34,1-78,1)	50,3 <sup>Abcd</sup> (41,2-77,7)
	RDA	62,3 <sup>ab</sup> (54-67)	58 <sup>ab</sup> (56-78)	42 <sup>d</sup> (40-45)	54 <sup>Abcd</sup> (49-55)	54 <sup>bcd</sup> (48-55)	56 <sup>Abcd</sup> (54-58)	77,5 <sup>Aa</sup> (77-77)	81,3 <sup>Aa</sup> (77-84)	45 <sup>cd</sup> (45-51)	65,5 <sup>bc</sup> (43,6-66,1)	51,3 <sup>Abcd</sup> (44,7-71,4)
FIB mg/dl	C	351 <sup>A</sup> (224-424)	351 <sup>A</sup> (224-424)	351 <sup>A</sup> (224-424)	351 <sup>A</sup> (224-424)	351 (224,4-424)	351 <sup>A</sup> (224-424)	351 (224-424)	351 (224-424)	351 (224-424)	351 <sup>A</sup> (224-424)	351 <sup>A</sup> (224-424)
	LDA	172 <sup>Bab</sup> (100-521)	158,6 <sup>Bb</sup> (122-216)	154 <sup>Bab</sup> (130-449)	141 <sup>Bb</sup> (76-354)	385 <sup>a</sup> (102-766)	177 <sup>Bb</sup> (103-511)	220 <sup>ab</sup> (124-467)	179 <sup>ab</sup> (123-488)	246 <sup>ab</sup> (76-478)	128 <sup>Bb</sup> (94-426)	158 <sup>Bb</sup> (110-269)
	RDA	187 <sup>Babc</sup> (154-203)	154 <sup>Bbc</sup> (141-158)	265 <sup>ABabc</sup> (105-357)	328 <sup>Aa</sup> (287-411)	208 <sup>abc</sup> (141-382)	154 <sup>ABabc</sup> (110-372)	146 <sup>c</sup> (92-201)	182 <sup>abc</sup> (127-224)	349 <sup>a</sup> (308-372)	269 <sup>ABab</sup> (136-454)	128 <sup>Bbc</sup> (126-190)

A, B, C and a, b, c; Different letters in the same rows and columns are statistically significant (Kruskall wallis,  $p < 0.05$ ). C, control, healthy animals; LDA, left displaced abomasum; RDA, right displaced abomasum; PT (prothrombin time), APTT (activated partial thromboplastin time), FIB (fibrinogen).

groups; whereas in the MPV concentration, a significant decrease ( $p < 0.05$ ) was detected after the operation in both groups and 96 hours after the operation only in the LDA group (Table 3).

## Discussion

In this study, a wide coagulation profile (PT, APTT, ATIII, Fibrinogen, D-Dimer, TAT, PAI-1, RBC and PLT indices) in cattle with a displaced abomasum (DA) was used to evaluate hemostatic dysfunction and DIC syndrome. The results of this longitudinal study (including pre-operative sampling time and 96-hour post-operative time) confirm that hemostatic abnormalities are present in cattle with DA and that results also shows that DIC may develop in cattle with DA.

Disseminated intravascular coagulation (DIC) is assessed by the combination of hemostatic test results. Coagulation monitoring measurements (PT, APTT, TT and fibrinogen concentration) have been optimized to determine factor deficiencies. It has been reported

that, in general, the DIC score is determined by moderate thrombocytopenia, prolonged PT, low fibrinogen and excess fibrinolytic products (FDP, D-Dimer) (Stokol 2012). In veterinary practice, it is stated that traditionally, DIC is diagnosed according to clinical and laboratory findings, and that typically, two clinical criteria (main disease and clinical symptoms) and two or more abnormal laboratory findings are required for diagnosis (Ritt et al. 1997). In another assessment, it has been reported that DIC diagnosis can be made based upon finding at least three components of the prolonged APTT and PT, presence of FDP, low fibrinogen concentration and thrombocytopenia profile (Estrin et al. 2006).

In studies on DIC in cattle with DA, it has been reported that, there was no difference between APTT and PT values before and after the operation in LDA cases (Ogurtan et al. 2003), TT, PT and APTT were prolonged, there was an increase in fibrinogen and D-Dimer, while a decrease was seen in ATIII and PLT levels (Sobiech et al. 2008), prolonged APTT ( $\geq 58.1$  sec) was encountered (Karakurum et al. 2009),

Table 3. Platelet indices in control, LDA and RDA groups.

Parameters	Groups	Sampling time, Median (minimum-maximum values)					
		Before operation	After operation	24 <sup>th</sup> hours	48 <sup>th</sup> hours	72 <sup>nd</sup> hours	96 <sup>th</sup> hours
PLT (K/mm <sup>3</sup> )	C	310 (243-412)	310 <sup>B</sup> (243-412)	310 (243-412)	310 (243-412)	310 (243-412)	310 (243-412)
	LDA	415 (139-1542)	645 <sup>A</sup> (259-1103)	344 (183-1089)	286 (223-393)	675 (138-1018)	413 (191-1456)
	RDA	359 (235-640)	789 <sup>A</sup> (259-948)	848 (258-1198)	614 (281-1040)	545 (504-671)	552 (396-719)
MPV (fL)	C	7,15 <sup>A</sup> (6,90-7,40)	7,15 <sup>A</sup> (6,90-7,40)	7,15 (6,90-7,40)	7,15 (6,90-7,40)	7,15 (6,90-7,40)	7,15 <sup>A</sup> (6,90-7,40)
	LDA	6,9 <sup>B</sup> (6,70-7,50)	6,9 <sup>B</sup> (6,60-7,20)	6,90 (6,70-7,30)	7,00 (6,80-7,40)	6,90 (6,60-7,50)	6,8 <sup>B</sup> (6,60-7,20)
	RDA	6,7 <sup>B</sup> (6,70-6,80)	6,9 <sup>B</sup> (6,80-6,90)	6,90 (6,90-7,40)	6,90 (6,90-7,20)	7,20 (7,00-9,80)	7,1 <sup>A</sup> (6,90-7,20)
PCT (%)	C	0,22 (0,17-0,30)	0,22 <sup>B</sup> (0,17-0,30)	0,22 (0,17-0,30)	0,22 (0,17-0,30)	0,22 (0,17-0,30)	0,22 (0,17-0,30)
	LDA	0,28 (0,10-1,06)	0,43 <sup>A</sup> (0,18-0,77)	0,24 (0,12-0,74)	0,19 (0,15-0,29)	0,49 (0,10-0,72)	0,30 (0,13-0,99)
	RDA	0,24 (0,16-0,44)	0,54 <sup>A</sup> (0,18-0,64)	0,59 (0,18-0,89)	0,42 (0,19-0,75)	0,38 (0,36-0,46)	0,39 (0,29-0,50)
PDW (%)	C	6,45 (5,50-7,40)	6,45 (5,50-7,40)	6,45 (5,50-7,40)	6,45 (5,50-7,40)	6,45 (5,50-7,40)	6,45 (5,50-7,40)
	LDA	6,40 (5,80-7,10)	6,20 (5,50-7,60)	6,20 (5,60-6,60)	6,40 (5,70-7,40)	6,10 (5,50-6,90)	6,20 (5,50-6,40)
	RDA	6,40 (5,60-6,50)	7,00 (6,10-7,00)	6,30 (6,30-7,70)	6,20 (5,40-6,60)	6,00 (5,90-6,50)	6,70 (6,30-6,70)

A, B, C; Different letters in the same line are statistically significant (Kruskall wallis,  $p < 0.05$ ).

C, control, healthy animals; LDA, left displaced abomasum; RDA, right displaced abomasum;

PLT, platelet; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet size distribution width.

and that an abnormal coagulation profile (prolonged APTT, FDPs increase and thrombocytopenia) was detected in two of the 10 cattle with LDA and three of the 10 cattle with RDA (Irmak and Turgut 2005).

In this research, D-Dimer and PAI-1 concentrations were determined to evaluate fibrinolytic system activation and inhibition. These test have been reported to be an important measure in determining the changes in fibrinolysis that are related to coagulopathy (Paloma et al. 1992, Matsuo et al. 2000). D-Dimer has been shown to be a good marker for ischaemia and inflammation, and plasma and peritoneal fluid D-Dimer level has been reported to be a good determinant for abdominal ischaemia conditions and inflammatory reactions related to hypercoagulopathy and increased fibrin formation in humans, dogs, horses and cattle (Collatos et al. 1995, Acosta and Bjorck 2003, Altinyollar et al. 2006, Delgado et al. 2009, Wittek et al. 2010). D-Dimer may provide useful information on the assessment of ischaemic damage and the severity of related complications (Grosche et al. 2012).

In this research, the D-Dimer level was determined as 731 (419-1061) ng/ml in the control group animals (Table 1). This value is higher than levels in healthy cows previously reported by other researchers (Sobiech et al. 2008, Wittek et al. 2010, Di Loria et al. 2012). In the authors' opinion, based on the high D-Dimer concentration determined in this research found within the post-partum 2-4 week period in the control and all experimental groups in this study, the effects of the post-partum period on this parameter (Boehlen et al. 2005, Epiney et al. 2005) must be taken into account. A significant increase was determined 72 and 96 hours after the operation in D-Dimer concentration in the control group compared to the experimental groups in cattle with DA (Table 1). This shows fibrinolytic system activation in cattle with DA and reflects that intravascular cross-linked fibrin degradation is at a significant level. In a study examining D-Dimer kinetics following abdominal surgery (Dindo et al. 2009), it was reported that D-Dimer remained at normal levels after the operation, significant increases at peak level were observed

on Day 7 and it returned to its normal level on Day 25 ( $\pm 14$ ). In this study, the statistically significant increases ( $p < 0.05$ ) in D-Dimer concentration, starting at 48 hours and detected at 72 and 96 hours, were attributed to the presence of hypercoagulation, ischaemia and inflammation (Acosta and Bjorck 2003, Altinyollar et al. 2006, Delgado et al. 2009, Wittek et al. 2010, Grosche et al. 2012), particularly during the post-operative period.

In humans, intra-abdominal adhesion formation following surgical trauma or peritonitis is attributed to decreasing peritoneal fibrinolytic capacity. Studies carried out on peritoneal biopsies during or after surgery indicate changes consistent with a decrease in tissue plasminogen activator (t-PA) level and an increase in the main fibrinolytic inhibitor PAI-1 (Holmdahl et al. 1998, Ince et al. 2002). After the DA operation, the thrombin formation increasing with reperfusion is expected to result in an increase in fibrin formation, and if the density is sufficient, a decrease in the level of fibrinogen in the circulation may be observed. At the end of the fibrinolytic activation, PAI-1 has been reported to increase I/R injury by inhibiting t-PA induced thrombolysis of microthrombi in ischemically-damaged tissue (Zhang et al. 1999, Nagai et al. 2005). It is stated that, the increase in PAI-1 indicates hypercoagulation and fibrinolysis inhibition (Collatos et al. 1994) and that permanently high PAI-1 activity is assessed as being an indicator of hemostatic regulation loss and insufficient treatment (Collatos et al. 1995). In this study, it was determined that the PAI-1 concentration remained high in the period before and after the operation compared to the control group ( $p > 0.05$ ) and was evaluated as the indicator for hypercoagulation and fibrinolysis inhibition in DA cases.

Coagulation and resulting thrombin formation activation is biochemically determined by measuring the TAT complex and ATIII concentration. In this research, ATIII concentration (mg/dl) was measured using a bovine specific ELISA kit and, to the authors' knowledge, has been reported for the first time in cattle. ELISA is a sensitive measure and evaluates all active/inactive anti-thrombin concentrations. In previous studies performed in cattle, in general, ATIII level is given as % activity. Since the coagulation activation during DIC is higher compared to values reported in previous studies in cattle, it is expected to lead to a drop in the ATIII level (Sobiech et al. 2008, Radwińska 2010, Di Loria et al. 2012, Sobiech et al. 2013). It is stated that due to the operation, particularly hemodilution, the ATIII level will be low and may reach a normal level on post-operative Day 5 (Sørensen 1996). Also, the drop in the ATIII level related to hemostatic system activation is expected to exhibit a decrease partially

consistent with TAT increase, despite not displaying a direct correlation with the TAT complex level (Levi and van der Poll 2010, Kloek et al. 2010). Thrombin in blood is controlled by its primary inhibitor ATIII and the TAT complex is formed. A high level of TAT complex in the blood is direct evidence of pro-coagulant activation and inhibitor utilization. In assessments involving hemostatic activation, particularly in DIC cases, its measurement is required. It has been reported that, the TAT complex level significantly increases in DIC cases (Levi and van der Poll 2010, Kloek et al. 2010). This parameter can exhibit changes related to the operation and on the first day of the operation, together with significant increases, it may gradually dip to low levels in the advancing post-operative period (Sørensen 1996), and since it is rapidly cleared from circulation, its high amounts may be temporarily observed (Pelzer et al. 1988). In this study, TAT level in healthy animals was found to be 19 (11.3-41.2) ng/ml. To the authors' knowledge, there is no study containing measurement of TAT concentration in cattle. In comparisons between serum TAT levels in the control group and the study groups, a high level was observed at all measurement times, except for the significant decrease ( $p < 0.05$ ) at 24 hours compared to before the operation only in the LDA group (Table 1). Increases in serum TAT concentrations were attributed to DIC development (Levi and van der Poll 2010, Kloek et al. 2010) and the decrease after the operation was associated with changes related to the operation (Sørensen 1996).

The main reasons for prolonged APTT is shown as increasing the digestion of coagulation factors during DIC (Sobiech et al. 2008). It was stated that, APTT is the most frequent profile abnormality encountered in cattle with LDA and RDA (Irmak and Turgut 2005) and also reported that APPT was prolonged in DA cases in cattle (Irmak and Turgut 2005, Karakurum et al. 2009). Conversely, in other study it was reported that APTT did not display a significant change in cattle with LDA (Ogurtan et al. 2003). Also, it has been expressed that prolonged PT is among the key indicators of development of severe DIC (Bick 1994, Çöl and Durgun 2011). The extrinsic path is activated by excess thromboplastic structures produced as a result of tissue damage, hypoxia, neoplasia, erythrocyte hemolysis, platelet aggregation or proteolytic enzymes (Muller-Berghaus et al. 2001). PT indicates the function of the extrinsic coagulation system and is prolonged during DIC due to increased consumption of coagulation factors (Çöl and Durgun 2011). While prolonged PT was determined in RDA cases (Irmak and Turgut 2005), PT was not prolonged in cattle with LDA (Ogurtan et al. 2003).

Results of this study have shown prolonged plasma PT (sec), PT (INR) and APTT times ( $p < 0.05$ ) in DA

cases compared to the control group (Table 2). These results are consistent with the operation and I/R damage response of the hemostatic system during and after the operation (Sørensen 1996), the increase in severity of DIC in the reperfusion period and the fact that PT may be prolonged during this period (Kloek et al. 2010). The results support opinions regarding prolonged PT (Irmak and Turgut 2005, Sobiech et al. 2008) and APTT (Irmak and Turgut 2005, Sobiech et al. 2008, Karakurum et al. 2009) determined in studies carried out in this field.

Fibrinogen is an acute phase protein, with the exception of severe activation of coagulation, its levels remain at normal levels and its amount in the plasma increases even in inflammatory diseases. It has been recorded that in clinical and experimental studies with severe DIC, the hypofibrinogenemia finding is diagnostically complementary and useful (Irmak and Turgut 2005, Levi and van der Poll 2010, Çöl and Durgun 2011). It was demonstrated that increase in fibrin concentration in the peritoneal fluid in cattle with LDA and reported extensive fibrin accumulation was observed on the surfaces of the abdominal organs that had changed position (Grosche et al. 2012). Fibrinogen is an important substrate for clot formation and low plasma concentration of fibrinogen may impair blood coagulation in patients with DIC (Radostits et al. 2000).

In this study, a significant decrease ( $p < 0.05$ ) was determined in the fibrinogen level in the LDA group compared to the control group at all measurement times except 2, 10, 24 and 48 hours after the operation; while in the RDA group a significant decrease ( $p < 0.05$ ) was observed before, after and 96 hours after the operation (Table 2). Low fibrinogen concentration is reported in DIC cases (Estrin et al. 2006, Jaillardon et al. 2012, Stokol 2012). Findings of this research are in contrast to previous studies (Irmak and Turgut 2005, Karakurum et al. 2009). Fibrinolysis is an important component of DIC. It is an indicator of fibrin degradation, as is an increase in D-Dimer and FDPs levels. In this research, hypofibrinogenemia and D-Dimer increase are findings complementing each other and are evaluated as a result of DIC development in DA cases.

In clinical practice, RBC and PLT indices are used as an indirect indicator of bone marrow activation. PLT indices include the following parameters: platelet count, mean platelet volume (MPV), plateletcrit (PCT) and platelet size distribution width (PDW) (Jones and Allison 2007, Yilmaz and Yeşilbağ 2008). Data on platelet indices in cattle is limited. Thrombocytopenia and high MPV indicates the megakaryocyte response to low platelet count and release of large platelets into circulation, whereas low MPV points to an insufficient

megakaryocyte count (Yilmaz and Yeşilbağ 2008, Kocatürk et al. 2010). In this research, the fact that an increase ( $p < 0.05$ ) was observed in the PLT and PCT concentrations after the operation in the experimental groups and a significant decrease in the MPV concentration ( $p < 0.05$ ) (Table 3), may be attributed to splenic contraction (physiological thrombocytosis), stress, blood loss and inflammation (reactive/secondary thrombocytosis) (Roland et al. 2014), and insufficient megakaryocyte response (Walz et al. 2001, Kocatürk et al. 2010).

In veterinary practice, there is no gold standard similar to the human medicine scoring system or model based on coagulation tests such as PT, APTT, D-Dimer, PLT and fibrinogen (Taylor et al. 2001). It is reported that, moderate thrombocytopenia, prolonged PT, low fibrinogen and increase in fibrinolytic products is observed (Stokol 2012) and that a diagnosis can be made by finding three components of the prolonged APTT and PT, FDP presence, low fibrinogen concentration and thrombocytopenia profile (Estrin et al. 2006). In veterinary practice, DIC is diagnosed by establishing two or more abnormal laboratory findings in the light of clinical and laboratory criteria (Ritt et al. 1997). Experts' view on the final diagnosis of DIC is that it can be confirmed in the light of criteria described by The International Society for Thrombosis and Hemostasis (ISTH) for DIC in humans. It is reported that this diagnosis can be made based upon coagulation activation (PT, APTT and PLT count), inhibitor utilization (AT, PC/Protein C and PS/Protein S) and fibrinolytic activity increase (D-Dimer, PLG/Plasminogen and  $\alpha 2$ -anti-plasmin) (Bick 1994, Taylor et al. 2001, Wiinberg et al. 2008).

In conclusion, in this study, coagulation data such as D-Dimer, PAI-1 increase, prolonged PT and APTT duration, which express fibrinolytic activation in the development of DIC, increases in TAT and ATIII concentration and changes during the treatment period have been evaluated as important evidence concerning development of DIC in DA cases. In this research, an abnormality was found at various times post operatively in six (D-Dimer, ATIII, PT (sec), PT (INR), APTT, FIB) coagulation parameters assessed in DA cases. These findings indicate that DA cases has hemostatic dysfunction and may develops DIC before operation and it can be continues in the post-operative period. This condition may effect the success of surgical operation in cattles with DA, since it can be signal for increased fibrin deposition and adhesions in the peritoneal cavity.



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