J Fac Vet Med
19/1-2(2000) 1-7

Effects Of Dobutamine, Methylprednisolone, Flunixin Meglumine And Enalapril In The Treatment Of Dogs With Experimentally Induced Septic Shock*

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Geliş Tarihi: 02.07.1999

Summary: In this study, it was aimed to compare the effects of various drugs in the treatment of dogs with experimentally induced septic shock. Hence, E.coli was given to each dog (30 dogs) via intravenous route at the dose of $5x10^9$ bacteria/kg. Septic shock criteries such as prolonged capillary refilling time (CFT), decreased peripheral pulsation quality, decreased plasma volüme, marked leukopenie and thrombocytopenie were observed within one hour after giving E.coli ($P<0.001$). In the treatment state, five groups each of which composed of six dogs were designated. Enrofloxacin and fluid were given to I^{th} group, dobutamine was given to II^{nd} group in addition to treatment of I^{st} group. Additionally, methylprednisolone, flunixin meglumine, and enalapril were added to III^{th}, IV^{th} and V^{th} groups, respectivelly. All dogs were monitored for clinical, hematological, serobiochemical parameters and survival time. While 3 dogs died in the I^{st} group, there was no death in the other groups in 5 days. As a result, it was concluded that positive effects of dobutamine were observed on circulatory functions and, when dobutamine was combined with flunixin meglumine, fluid and antibiotic; the combination was found to be the most effective therapy in the management of septic shock.

Key Words: Septic Shock, Endotoxemia, Dog

Köpeklerde Deneysel Olarak Oluşturulan Septik Şokun Sağaltımında Dobutamine, Flunixin Meglumine, Methylprednisolone ve Enalapril'in Etkileri

Özet: Bu araştırmada, deneysel olarak septik şok oluşturulan köpeklerin sağaltımında farklı ilaçların etkilerinin karşılaştırılması amaçlandı. Bu amaçla köpeklerin her birine (30 köpek) intravenöz yolla $5x10^9$ adet/kg dozunda E.coli verildi. E.coli verildikten sonra ortalama bir saat içinde ateş, kapillar dolma süresinde uzama, periferal nabız kalitesinde zayıflama, plazma volümünde azalma, lökopeni ve trombositopeni ($P<0.001$) gibi septik şok kriterleri saptandı. Sağaltım aşamasında her biri 6 köpek içeren 5 farklı grup oluşturuldu. Birinci grupta enrofloxacin+sıvı; II.grupta bu sağaltıma ilave olarak dobutamin uygulandı. II.gruptaki bu kombinasyona III.grupta metilprednisolon, IV.grupta flunixin meglumin, V.grupta ise enalapril eklendi. Köpeklerin tümü klinik, hematolojik, serum biyokimyasal parametreleri ve yaşama süreleri yönünden gözlendi. Beş günde I.grupta 3 köpek ölürken, diğer gruplarda hiç bir ölüm olayına rastlanmadı. Sonuç olarak, dobutaminin dolaşım fonksiyonları üzerine olumlu etkilerinin olduğu; dobutaminin flunixin meglumin, sıvı ve antibiyotik ile kombine edildiğinde, bu kombinasyonun septik şok sağaltımındaki en etkili tedavi olduğu kanısına varıldı.

Anahtar Kelimeler: Septik Şok, Endotoksemi, Köpek

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* Bu çalışma 'Köpeklerde Deneysel Olarak Oluşturulan Septik Şokun Sağaltımında Dobutamine, Flunixin Meglumine, Methylprednisolone ve Enalapril'in Etkileri' başlıklı doktora tezinin özetidir.

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Introduction

Septic shock is defined as a peripheral circulatory failure and cell death due to inadequate tissue perfusion and seconder effects of infection process[1]. What has been called sepsis, septic syndrome, or septic shock in the past is now being renamed systemic inflammatory response syndrome (SIRS)[2,3]. Septic shock primarly caused by gram-negative bacterias[4] is a common complication in severe diseases such as diffuse peritonitis, parvo viral enteritis and hemoragic gastroenteritis in dogs[5,6].

Releasing of a number of endogenous mediators are initiated in response to the presence of bacteria or endotoxin in the bloodstream[7]. Endogen mediators, which occur myocardial depression and hypotension, lead to cardiovascular failure[8,9].

While fever, hypotension, shortened CFT, tachypnea, tachycardia are monitored during hyperdynamic phase in the earlier stage; hypotension and prolonged CFT are monitored during hypodynamic phase in the late stage of septic shock[2,4]. Marked leukopenie, neutropenie, and thrombocytopenie are determined as indicators of endotoxemia in the early stage. Criteries of septic shock including the results of clinical and laboratory examinations are used in the diagnosis[10].

Succes in the treatment of septic shock depends on early diagnosis, elimination of sources of sepsis and providing adequate hemodynamic support[11]. While highly effective antibiotics are used against microorganisms, sympathomimetics, corticosteroids, nonsteroidal antiinflammatory drugs or vasodilators can be combined with intravenous fluid therapy so as to provide hemodynamic support[4,12]. However, it has been still reported that the role of corticosteroids and vasodilators in the management of septic shock remains a controversial subject[10].

In this study, it was aimed to compare the effects of dobutamine, methylprednisolone, flunixin meglumine or enalapril combined with antibiotic and fluid, and to find the effective therapy in the treatment of dogs with experimentally induced septic shock.

Material and Methods

Clinically and hematogicaly healthy, of different age, sex, and weight, cross-breed, 30 dogs were used as materials. E.coli organisms were prepared, and given slowly via i.v. route at the dose of $5x10^9$ bacteria/kg over five minute periods. Criteries of septic shock were observed within one hour. Thirty dogs were divided into five groups, each of which consisted of six dogs, in the treatment stage:

- GROUP I (n=6): Enrofloxacin + Ringesol (control group)
- GROUP II (n=6): Enrofloxacin + Ringesol + Dobutamine
- GROUP III (n=6): Enrofloxacin + Ringesol + Dobutamine + Methylprednisolone
- GROUP IV (n=6): Enrofloxacin + Ringesol + Dobutamine + Flunixin meglumine
- GROUP V (n=6): Enrofloxacin + Ringesol + Dobutamine + Enalapril

For fluid therapy, ringesol (Vilsan) was given at the dose of 60 ml/kg in the shock stage and maintaned with 20 ml/kg at the 12^{th}, 24^{th}, 36^{th} and 48^{th} hours of shock in all groups. Enrofloxacin (Baytril fl. %10, Bayer) was chosen on the basis of antibiogram and administred (5mg/kg, i.v.) twice daily for five days. Dobutamine (Dobutrex 250mg fl., Lilly) in %5 dextrose was infused of 10mcg/kg/min via i.v. route 5 minutes after fluid and antibiotic therapy had begun. Infusion of dobutamine was stopped 10 minutes after peripheral pulsation quality and heart beat returned normal. Methylprednisolone (Prednol-L 250mg fl., Mustafa Nevzat), 30 mg/kg, was given only a single dose by i.v. route at the beginning of shock therapy. Flunixin meglumine (Finadyn 20cc fl., Schering) (1.5 mg/kg) was administered intravenously in the shock stage, the same dose was repeated at the 2^{nd} and 12^{th} hours of shock. Utilization of enalapril (Enalap 10mg tb., Saba) was started at the 24^{th} hour after hypotansion had been controlled and it was used twice daily 0.5mg/kg orally.

Clinical examinations including body temprature, heart and respiratory rate, peripheral pulsation quality and CFT were carried out before giving E.coli, in the shock stage and at the 1^{st}, 4^{th}, 12^{th}, 24^{th}, 36^{th}, 48^{th}, 72^{th}, 96^{th} and 120^{th} hours. Blood samples were taken for hematologic and biochemical examinations at the same times of shock. Specific analyses include WBC count, neutrophil rate, Hct, Hg concentration and platelet count. WBC counts and platelet counts were performed, using an automated cell counter

(Serono). Neutrophil rate was performed on May Grünwald-Giemsa-stained blood smear. Serum concentrations of total protein, albumine, urea, and glucose; activities of ALT, AST, and CK; and plasma concentrations of lactic acid were determined by using Thecnicon Dax-72. Intra arterial blood pressure tecnics, which require anesthesia, were not used for progress of septic shock and effects of drugs could be accurately monitered clinicaly whithout anesthesia. Therefore, peripheral pulsation quality observed through palpation of arteria femoralis was relatively interpreted, as reported in the previous researches[4,13]. Relative changes in plasma volume were calculated from hematologic values (Hct and Hg concentration), using accepted formulas[14,15].

Mental status and survival times of all dogs were monitored throughout the study. Repeated measures of clinical, hematological and biochemical parametres were analysed by using two-way ANOVA in Minitab Statistic Programme. Differences between pre-shock stage and shock stage of all 30 dogs were compared by t-student test. Scores of peripheral pulsation quality were analysed using Kruskal-Wallis Non-parametric Test in Instate Statistic Programme. The control of differences between groups were performed by use of Dunn's Multiple Comparison Test.

Results

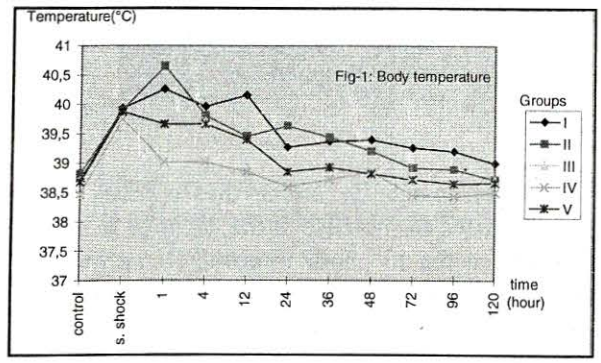
After a short time of giving E.coli, all dogs showed abnormalities of general status such as mental depression, vomiting, tenesmus, diarrhae (sometimes bloody) and septic shock occured roughly within one hour. Statistical results of clinical, hematological and biochemical parameters of all dogs before septic shock and at the shock stage are shown in Table I.

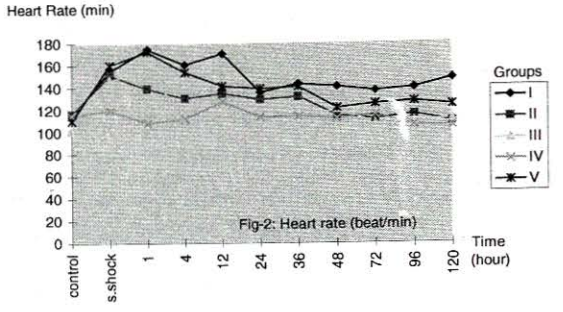
Figure-1 presents the body temparatures of all five groups of this study. Body temperature started to decrease significantly at the 1st hour and returned normal limits at the 24th hour of our study in group IV ($p<0.01$). Figure-2 shows the changes in mean heart-rates from control time through 120 hours. Although increasing until the 1st hour in group I, III and V, heart rates countinously remained at high rates in group I. Changes of CFT can be seen in figure-3. During the study, CFT never decreased below 2 second in group I and V ($p<0.001$). It was observed that CFT shortened from the beginning of the 36th hour in group II, 1st hour in group III and IV, and 72th hours in group V ($p<0.001$). As seen in figure-4, group III, when compared with other groups, had the best scores of peripheral pulsation quality at the 4th, 24th and 48th hour to group I and V ($p<0.05$), at the 12th and 72th hour to group I ($p<0.05$).

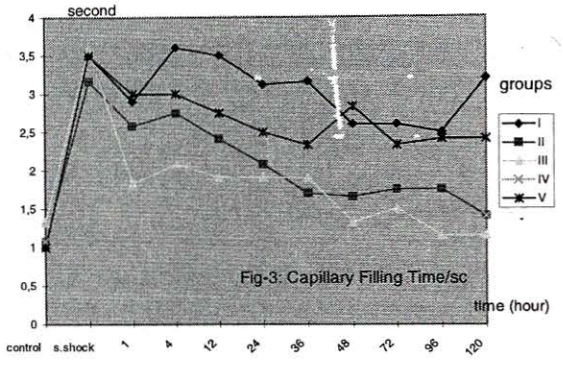
Table I. Statistical results of clinical, hematological and biochemical parameters of all dogs with septic shock

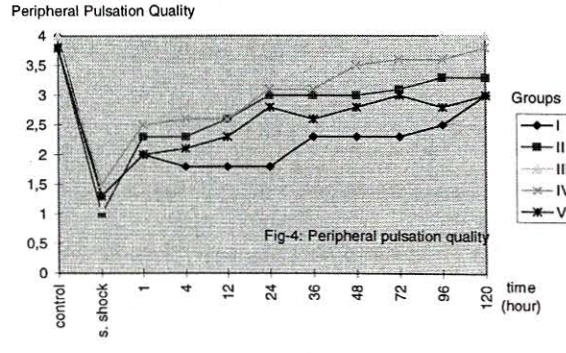
Parameters	Control	Septic Shock Stage
Temperature (°C)	38.6 ± 0.08	39.7 ± 0.17***
Heart Rate (min)	111.33 ± 3.33	146.31 ± 7.53***
Respiratory Rate (min)	18.46 ± 0.90	33.47 ± 1.85***
Capillary Refilling Time(sc)	1.10 ± 0.05	3.45 ± 0.12***
WBC (mm^3)x10^3	8.69 ± 0.52	2.25 ± 0.33***
Neutrophil (%)	74.63 ± 2.94	36.07 ± 5.43***
Platelet (mm^3)x10^3	340.90 ± 40.40	98.20 ± 17.90***
PCV (%)	41.92 ± 1.19	48.60 ± 1.44***
Hg (gr/dl)	14.03 ± 0.42	15.86 ± 0.50**
Plasma volume (%)	100.00 ± 0.00	75.87 ± 3.04***
Total protein (gr/dl)	6.58 ± 0.13	6.14 ± 0.15
Albumine (gr/dl)	3.36 ± 0.23	3.11 ± 0.10
Urea (mg/dl)	31.18 ± 3.91	34.87 ± 3.00
Glucose (mg/dl)	86.21 ± 4.72	95.04 ± 6.91
ALT (u/l)	47.00 ± 13.60	84.00 ± 17.70
AST (u/l)	36.23 ± 2.90	213.10 ± 41.60***
CK (u/l)	224.20 ± 29.60	1119.32 ± 263.42
Lactic acid (mg/dl)	2.90 ± 0.28	6.95 ± 0.77***

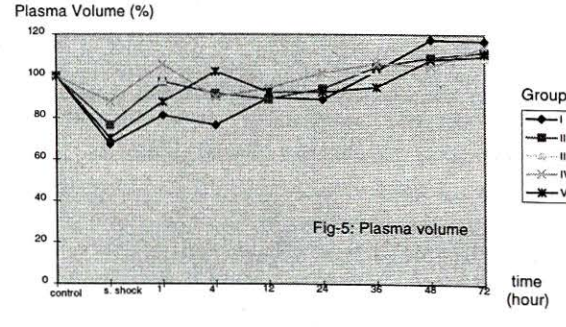
** $p<0.01$ *** $p<0.001$











Decreased WBC counts due to shock in all groups started to increase at the 4th hour in group II and V, at the 12th hour in group III, at the 24th hour in group I and group IV ($p<0.001$). Decreased neutrophil rate of shock started to increase at the 1st hour in group I and II, at the 4th hour in group III and V, at the 12th hour in group IV ($p<0.001$). Decreased platelet counts of shock started to increase at the 1st hour, but thrombocytopenie continued in all groups during the study (Table II). It was observed that changes of Hct and Hg values seemed similar to each other. Decreased plasma volumes of shock started to increase, when compared with control value, at the 36th hours in group I and II, at the 4th hour in group III (Fig.5).

All groups showed unimportant changes of total protein and albumine concentrations during the study. In spite of treatment, urea concentration increased until the 24th hour in all groups and then it reached the highest concentration (114.3±50.8) in group I . Although decreasing at the shock stage in group I and II, glucose concentration increased in other groups.

One dog at the 1st hour, two dogs after at the 12th and 24th hour died in group I, but there was no death in the other groups during the study. The rest of the dogs completely recovered by the end of the study.

Discussion

Septic shock is characterized by significant and rapidly progressing clinical- labarotory results[15]. In this research, clinical and hematological findings such as increased body temparature, increased heart and respiratory rate, prolonged CFT, decreased peripheral pulsation quality, decreased WBC count, decreased platalet count and decreased neutrophil rate indicated septic shock process in all dogs ($p<0.001$).

Increased body temparature at the shock stage returned to normal from 12th hour in group III, from 1st hour in group IV. This result shows that flunixin meglumine controlled the body temparature within a short time. This is probably due to the fact that flunixin meglumine immediately prevents the synthesis of prostaglandins[16] and that methylprednisolone reduces the synthesis of prostaglandins by stimulating the formation of an inhibitor molecule lipocortin[17].

In addition to 1st group's therapy, dobutamine was given in group II. Therefore, increased heart rate at the shock stage dropped gradually in group II. Decreasing of heart rate started at 1st and 4th hour in group III and IV, in which flunixin meglumine and methylprednisolone improving the circulatory system were used in addition to dobutamine.

Tablo II. Statistical results of hematological and biochemical parameters of all dogs with septic shock

PARAMETERS		CONTROL $\overline{X} \pm Sx$	S. SHOCK $\overline{X} \pm Sx$	1th hour $\overline{X} \pm Sx$	4th hour $\overline{X} \pm Sx$	12th hour $\overline{X} \pm Sx$	24th hour $\overline{X} \pm Sx$	36th hour $\overline{X} \pm Sx$	48th hour $\overline{X} \pm Sx$	72th hour $\overline{X} \pm Sx$	96th hour $\overline{X} \pm Sx$	120th hour $\overline{X} \pm Sx$
Total WBC Count (x10³/mm³)	I	b 7.283±0.860	b 2.216±0.621	b 3.900±0.915	b 6.82±1.591	abAB 11.700±2.536	aBC 180.8±5.582	a 21.300±3.117	a 20.233±4.330	ab 13.400±1.907	ab 11.33±2.351	ab*** 12.300±2.200
	II	ab 9.516±1.400	b 3.216±1.291	ab 9.950±5.671	ab 17.783±9.164	abAB 26.366±10.07	aABC 35.200±11.73	ab 26.033±10.15	ab 24.400±7.132	ab 11.700±0.557	ab 10.733±2.70	ab* 11.583±3.021
	III	c 8.883±1.141	c 1,983±0.505	c 4.400±1.559	bA 19.216±4.06	bA 28.916±3.534	aA 55.116±4.151	ND	b 28.033±4.078	b 10.66±4.078	c 8.783±0.833	c*** 9.416±0.629
	IV	acde 7.983±1.545	e 1.283±0.401	e 2.233±0.625	de 4.466±1.160	cdeB 6.616±1.249	abcC 19.950±2.974	a 17.440±3.562	ab 17.350±3.627	abcd 12.700±1.851	abcde 96.460±2.024	abcde*** 12.140±5.520
	V	bdef 9.800±0.813	f 2.566±0.527	bcdef 7.333±3.079	bcde 17.416±4.528	bcdAB 24.216±5.696	aAB 42.700±4.820	ab 27.633±1.675	be 26.250±4.271	bedef 13.716±1.889	ef 9.616±0.594	ef*** 9.483±0.359
Neutrophil (%)	I	a 68.00±8.49	b 18.67±8.52	a 59.40±11.30	aA 83.80±2.71	a 89.20±3.88	a 91.25±3.59	a 90.50±5.50	a 85.67±5.67	a 80.00±2.89	a 85.67±3.84	a*** 86.00±6.00
	II	a 78.50±8.64	b 46.70±12.5	a 78.83±5.50	aA 88.83±2.24	a 94.17±1.51	a 93.17±1.35	a 92.00±1.10	a 90.83±1.08	a 86.83±3.38	a 86.83±3.29	a*** 86.60±3.75
	III	bc 79.73±2.01	a 43.80±13.00	ab 57.50±12.60	cA 85.67±3.69	c 90.67±2.39	c 96.83±0.54	ND	c 88.50±0.80	bc 83.50±3.31	bc 82.40±2.82	bc*** 84.60±2.66
	IV	a 82.67±3.08	b 21.33±8.97	b 28.50±14.20	bB 42.2±16.20	a 83.00±2.95	a 95.00±0.31	a 94.80±0.58	a 93.20±2.40	a 88.40±1.57	a 87.60±1.03	a*** 84.00±3.58
	V	abc 64.17±6.21	a 49.80±14.10	ab 58.70±16.10	bcA 83.67±5.54	bc 88.00±3.72	c 96.17±1.11	bc 94.33±1.67	c 91.33±1.52	abc 79.33±4.33	abc 77.17±2.93	abc*** 80.17±2.37
Thrombocyte (X10³)	I	a 2.40±0.68	b 0.21±0.08	ab 1.03±0.34	ab 1.27±0.38	ab 1.11±0.38	ab 1.08±0.35	ab 1.15±0.72	ab 0.49±0.11	ab 1.01±0.08	ab 0.99±0.191	ab* 2.12±0.60
	II	a 3.87±0.91	b 1.04±0.32	b 2.02±0.48	b 1.54±0.37	b 1.23±1.44	b 1.10±0.27	b 0.86±0.15	b 0.86±0.21	b 1.51±0.26	ab 2.41±0.37	ab*** 2.09±0.53
	III	a 3.71±1.41	b 0.58±0.21	ab 1.31±0.54	ab 1.98±0.76	ab 1.82±0.68	ab 1.05±0.42	ND	b 0.69±0.25	ab 1.62±0.36	ab 2.59±0.67	ab* 2.76±0.50
	IV	a 3.74±0.80	ab 2.00±0.49	ab 2.12±0.55	ab 2.05±0.40	b 1.44±0.039	b 1.53±0.28	b 1.45±0.43	b 1.49±0.37	ab 2.54±0.74	ab 2.10±0.33	ab* 2.91±0.52
	V	a 3.30±0.70	b 0.86±0.36	ab 1.77±0.36	ab 2.20±0.57	ab 2.04±0.47	b 1.27±0.26	b 0.66±0.72	b 0.89±0.29	b 0.87±0.26	ab 1.50±0.59	ab** 2.10±0.49
CK (U/L)	I	b 371.20±116.	aA 2996.6±519.4	ab 1503.75±302	b 902.50±283.1	ab 1352.25±505.	ab 2526.00±1540.	ND	ab 1105.33±330.	ab 850.66±485.7	b* 346.66±101.9	ND
	II	247.20±63.7	B 504.25±147.7	425.40±137.9	519.50±59.70	566.20±93.30	907.33±224.7	ND	366.33±126.7	421.33±200.8	639.80±236.7	ND
	III	170.80±49.2	B 468.83±138.3	673.20±372.9	353.40±113.8	269.00±109.2	253.20±101.4	ND	525.16±188.8	430.80±99.80	369.30±70.30	ND
	IV	157.20±29.2	B 228.70±72.50	255.00±54.50	468.83±143.75	426.50±160.05	626.33±259.10	ND	301.83±139.45	297.40±99.60	388.80±69.70	ND
	V	186.80±30.0	B 1030.00±375.	1144.70±784.	634.00±212.2	875.00±273.9	2000.17±653.	ND	1010.22±395.	649.00±89.10	746.66±471.8	ND
Lactic Acide (mg/dl)	II	b 3.15±0.52	a 7.45±1.06	a 8.20±1.03	ab 4.87±1.33	ab 4.45±1.33	b 2.80±0.59	ND	b 1.90±0.63	b 1.10±0.30	b 1.80±0.35	b*** 1.63±0.33
	IV	bc 2.65±0.26	a 6.30±1.26	ab 4.87±1.03	bc 3.50±0.51	abc 3.95±055	bc 3.05±0.49	ND	c 2.10±012	c 1.82±0.25	c 1.82±0.41	c*** 2.02±0.35

ND: Not determlnatcd a, b, c, d, e, f: Differences between the values involving different letters on the same line is found to be important

A, B: Differences between the values involving different letters on the same column is found to be important * $p<0.05$ ** $p<0.01$ *** $p<0.001$

In our study in all groups CFT was over 3 second at shock stage ($p<0.001$) and accepted as a sign of peripheral circulatory failure. Decreasing of CFT started from 1st hour in group III and IV. This probably occured when dobutamine was combined with flunixin meglumin or methylprednisolon. In addition, dobutamine has been reported to improve cardiac output[1,18]. Although vasodilators such as enalapril may be usefull in septic shock to improve tissue perfusion after blood volume restoration[1], dobutamine + enalapril combination in group V didn't affect as expected. It may be related to side effects of enalapril such as peripheral pooling of blood and decreasing of cardiac output leading to hypotension[12]. CFT was observed within normal range at the 1st hour in group III and it was the earliest time in our study. It may be related to benefit effects of corticosteroids increasing vascular membran preservation and cardiac output[2]. In group IV, CFT started to become in normal range at the 24th hour, because flunixin meglumine is effective due to its enhancing sistemic vascular resistance and cardiac output[2].

If the femoral pulse is absent or very difficult to detect, that blood pressure is 50mmHg or less is reported[13]. Therefore, weaked peripheral pulsation quality, accepted as a criteria of septic shock, was interpreted as hypotension in all groups ($p<0.001$). After treatment, peripheral pulsation quality was better in the others than group I; this may be related to effects of dobutamine as it increases cardiac output and makes vasoconstriction[18]. Peripheral pulsation quality was better in group III and IV than group I and V. This may be because of the fact that methylprednisolone and flunixin meglumine potantiate the effects of sempatomimetics given at the same time[2,19], and that enalapril has hypotensive effects[1,18,20].

Endotoxemia, the early stage of which is characterized by leukopenia, neutropenia and thrombocytopenia, usually produces a neutrophilic leukocytosis in the late stage[2,14,21]. Likewise, neutropenia and leukopenia at the shock stage turned to neutrophilic leucocytosis from 24th hours in the present study. The highest level of WBC count was observed in group III. This may be associated with the effects of corticosteroid, which inhibits the mediators (LT, C5a) playing role in the leucocyte adhession[9].

Thrombocytopenia typically occurs with septic shock[22]. Although thrombocyte count, which was decreased at the septic shock stage, increased from 1st hours in all groups, did not reach to control value until the 120th hours. This was interpretted as an indicator of proggressive thrombocytopenia. However, it is reported that corticosteroids increase the thrombocyte count[1,4], the changes of thrombocyte counts were not significant between group III and the others.

Hct and Hg values and albumine concentrations partly decreased especially at the 1st and 4th hours of the study, plasma volume increased, though. This is associated with fluid given to treat of the hemoconcentration in the shock stage. Also, plasma volume at the 4th hour in the group III and IV was better than group I. Since methylprednisolone and flunixin meglumine improve vascular permeabilty via mediator inhibition[2,22].

It is reported that urea concentration may increase due to decreasing renal blood flow in the hypovolemic and shock state[22]. The increased urea concentration until the 24th hours ($p<0.01$) in all groups shows that acute tubular necrosis as well as renal hypoperfusion may be effective.

Although corticosteroids are able to increase the glucose concentration by means of hepatic glucogenesis[21], the changes of glucose concentration was not significant between group III and the others. On the other hand, hypoglycemia, determined at the 4th, 12th, and 24th hour in group I, may be attributed to severity of shock and liver damage detected by increasing of ALT activity at the same times. The reason why the increase of ALT activity became much less in group III than other groups may be related to effects of methylprednisolone such as stabilisation of cell membrans. In spite of increasing AST activity, ALT activity was in normal range. The reason for this may be the increase of heart and skeletal muscle damage.

CK activity was the highest in group I, but the smallest in group III and IV, as methylprednisolone and flunixin meglumine improve blood flow and microcirculation[21,22]. The increase of lactic acid concentration was much less in group IV than that in group II. Since flunixin meglumine not only prevents from hypotension by inhibition of PG's, but also increases cardiac output[23]. Also, dobutamine enhances the effects of flunixin meglumine[24].

In this study, while positive effects of dobutamine were observed on circulatory function, enalapril was not able to be effective. Superiority of methylprednisolone given group III

was not significant in all except from group I. Also, it was observed that methylprednisolone led to severe neutrophilic leukocytosis. The general conditions of the animals were better and the fever was controlled earlier especially in the flunixin meglumine given group. It was concluded that the best result was obtained with antibiotic + fluid + dobutamine and flunixin meglumine combination.

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