Turkish Journal of Veterinary & Animal Sciences

Volume 27 | Number 2 Article 9

1-1-2003

Effects of Hypertonic Sodium Chloride, Hypertonic Sodium Chloride + Sodium Bicarbonate and Hypertonic Sodium Chloride + Ringer's Lactade Solution in the Treatment of Dogs with Experimentally Induced Endotoxaemia

HASAN BATMAZ

ZEKİ YILMAZ

AYŞE TOPAL

O. SACİT GÖRGÜL

SEZGİN ŞENTÜRK

Turk J Vet Anim Sci
27 (2003) 339-347

Research Article

Effects of Hypertonic Sodium Chloride, Hypertonic Sodium Chloride + Sodium Bicarbonate and Hypertonic Sodium Chloride + Ringer's Lactate Solution in the Treatment of Dogs with Experimentally Induced Endotoxaemia*

Hasan BATMAZ, Zeki YILMAZ
Department of Internal Diseases, Faculty of Veterinary Medicine, Universty of Uludağ, Bursa - TURKEY
Ayşe TOPAL, O. Sacit GÖRGÜL
Department of Surgery, Faculty of Veterinary Medicine, Universty of Uludag, Bursa - TURKEY
Sezgin ŞENTÜRK
Department of Internal Diseases, Faculty of Veterinary Medicine, Universty of Uludağ, Bursa - TURKEY

Received: 23.08.2001

Abstract: The aim of this study was to compare the effects of isotonic sodium chloride (ISS-0.9%), hypertonic sodium chloride (HSS-7.2%), HSS + lactate ringer solution (LRS) and HSS + sodium bicarbonate solution (SBS-1.3%) in the treatment of dogs with endotoxaemia. Endotoxaemia was induced by slow injection of a 1 mg/kg/i.v. dose of *E. coli* endotoxin (0111:B4). At the treatment stage, four groups, each composed of six dogs, were formed and a different treatment plan was carried out in each group: ISS, HSS, HSS + LRS and HSS + SBS. Clinical, haematological and biochemical examinations were performed before and after endotoxaemia.

Hypotension (MAP < 60 mm Hg), leukopaenia and trombocytopaenia were observed during endotoxaemia in all dogs. MAP and plasma volume were increased in all groups except the ISS group. HCO^-_3 values were increased in the HSS + SBS group and decreased in the other groups. Therefore, it was concluded that the HSS + SBS combination was the most effective model of fluid therapy in the treatment of dogs with endotoxaemia.

Key Words: Sodium chloride, lactate ringer, sodium bicarbonate, endotoxaemia, dog

Deneysel Olarak Endotoksemi Oluşturulan Köpeklerin Tedavisinde Hipertonik Sodyum Klorür, Hipertonik Sodyum Klorür + Sodyum Bikarbonat, Hipertonik Sodyum Klorür + Laktatlı Ringer Solusyonlarının Etkileri

Özet: Bu çalışmada endotoksemili köpeklerin tedavilerinde isotonik sodyum klorür (% 0,9 ISS), hipertonik sodyum klorür (% 7,2 HSS), HSS + laktatlı ringer solusyonu (LRS) ve HSS + sodyum bikarbonat solusyon (% 1,3 SBS)'larının etkilerinin karşılaştırılması amaçlandı. *E. coli* endotoksini'nin (0111:B4) 1 mg/kg/iv dozunda yavaş enjeksiyonu ile endotoksemi oluşturuldu. Tedavi aşamasında herbiri altı köpek içeren dört grup oluşturuldu ve herbirine farklı bir tedavi planı uygulandı. ISS, HSS, HSS + LRS ve HSS + SBS. Endotoksemi öncesi ve sonrasında klinik, hematolojik ve biyokimyasal muayeneler gerçekleştirildi.

Endotoksemi anında tüm köpeklerde hipotansiyon (MAP < 60 mm Hg), lökopeni ve trombositopeni saptandı. MAP ve plazma volümü ISS grubu haricinde diğer gruplarda arttı. HCO^-_3 değeri HSS + SBS grubunda artmasına rağmen, diğer gruplarda azaldı. Bu nedenlerle, endotoksemili köpeklerin tedavilerinde en etkin sıvı tedavi modelinin HSS + SBS kombinasyonu olduğuna karar verildi.

Anahtar Sözcükler: Sodyum klorür, laktatlı ringer, sodyum bikarbonat, endotoksemi, köpek

Introduction

Endotoxaemia is still one of the most common causes of death in humans and animals in intensive care units (1). Vasoactive substances such as histamine, tumour necrosing factor and leukotriens released by endotoxin in the bloodstream lead to hypovolaemia and decreased

* U.Ü. Araştırma Fonu tarafından desteklenmiştir (Proje no: 98/24).

cardiac output (2-8). Reduced cardiac output and hypovolaemia could be improved by intravenous fluid replacement therapy (1,2,8-12).

Crystalloid solutions such as 0.9% saline or lactated ringer's solution are the first line of therapy in the management of endotoxaemia (3,7,10,13). Isotonic crystalloid solutions should be cautiously used because of the development of the increased permeability of pulmonary and peripheral microvessels (10,14,15). Therefore, it is important to consider monitoring patients with central venous pressure measurement (CVP), and adjust therapy accordingly in order to minimise pulmonary oedema (16). In recent years, small volumes (3-5 ml/kg) of hypertonic saline (3-7.5%) have been used to successfully resuscitate dogs with experimentally induced endotoxaemia (2,17,19). The documented beneficial effects of hypertonic saline include increases in mean systemic arterial pressure (MAP), cardiac output, cardiac contractility, and stroke volume; while total peripheral vascular resistance and pulmonary vascular resistance decrease, and mean circulatory filling pressure increases. The administration of hypertonic saline has potential disadvantages which include the risk of hypernatraemia and hyperosmolality, cardiovascular collapse and haemolysis (9,20,21)

In this study, our aim was to find the most effective fluid therapy in the management of dogs with endotoxaemia.

Materials and methods

Dogs: Clinically and 24 haematologically healthy dogs, crossbreed, of different age (2-5 years), sex (13 male, 11 female), and weight (8-20 kg), were used as materials.

Experimental design: Xylazine HCl (Rompun-Bayer) was used as premedication at a dose of 2 mg/kg/IM to each dog. Induction was induced by thiopental sodium (10 mg/kg/IV) (Pentothal sodium-Abbott). An endotracheal tube was inserted and connected to the anaesthetic machine for the administration of isoflorane 2% (Forane-Abbott) in O_2 (22,23). The dogs were allowed to breathe spontaneously from O_2 flow at 4 l/min. Arteial (Braun, 18G) and CVP catheters were surgically inserted into the right femoral artery for the continuous measurement of femoral artery pressure and the serial determination of arterial blood gases, and into the vena jugularis for the determination of CVP, respectively. An aneroid sphygmanometer was also used for the measurement of MAP. Heart and respiratory rates and body temperature were determined by pulse oximeter (Vet/Ox 4403, SDI Co., USA).

Endotoxaemia was induced by slow (over 5 min) intravenous injection of a 1 mg/kg dose of *E. coli* endotoxin (lipopolysaccharide *Escherichia coli* 0111:B4-Sigma) (22-24). After 25-40 min of endotoxin adminstration, clinically and haematologically the criteria of endotoxaemia were observed. The main criterion of endotoxaemia was MAP ≤ 60 mmHg (8,14). At the treatment stage, four groups, each composed of six dogs, were formed and a different treatment plan was carried out in each group, as below:

Groups	n	Fluids	Dose
ISS	6	Isotonic Sodium Chloride Solution (ISS)-0.9%	32 ml/kg,IV
HSS	6	Hypertonic Sodium Chloride Solution (HSS)-7.2%	4 ml/kg, IV
HSS + LRS	6	HSS + Lactate Ringer's Solution (LRS)	HSS-4 ml/kg, IV LRS-15 ml/kg, IV
HSS + SBS	6	HSS + Sodium Bicarbonate Solution (sbs)- 1.3%	HSS-4 ml/kg,IV SBS-15 ml/kg, IV

ISS (0.9%) and HSS (7.2%) were administered at a rate of 32 ml/kg and 4 ml/kg, respectively (25). LRS (15 ml/kg, IV) and SBS (1.3%, 15 ml/kg, IV) were used as a maintenance fluid 45 min after the discontinuation of HSS administration in the HSS + LRS and HSS + SBS groups, respectively.

Sample collection and measurements: Angio-chatt (Venflon 2, 18-20G) was placed into the vena cephalica antebrachie for fluid therapy and the determination of serial haematological and biochemical examinations. Clinical examinations including body temperature (T), heart rate (HR), respiratory rate (RR), capillary filling time (CFT), mean arterial pressure and central venous pressure were carried out just before giving toxin (base line) at endotoxaemia, and at 10, 30, 75 min, and 2 and 4 h after treatment (6,13). Blood samples were collected at the same points during the monitoring period. Haematologically, white blood cell (WBC) count, haematocrit (PCV), haemoglobin (Hg) and platelet count (PLT) were performed by an automated cell counter (Serono). Relative changes of plasma volume were calculated from haematological values (PCV and Hg), using accepted formulas (17). Blood gas measurements (pH, pCO_2, BE, HCO^-_3, and tCO_2) were performed by using heparinized haematocrit tubes (Chrion Diagnostic-blood gas analyser) (22). Total protein (TP), sodium (Na) (Axio-m) and chloride (Cl) (Teco Diagnostic) levels were

measured by biuret methods and spectrophotometrically, respectively.

Statistical analysis: Variables involving repeated measures were analysed with multivariate repeat-measures ANOVA. When a significant ($p < 0.005$) group or time interaction was observed, additional testing was performed using Duncan's test to determine differences within groups and between groups. Variables measured once during the study were evaluted for between group differences using a t-test.

Results

After 25-40 min of giving *E. coli* toxin, the criteria of endotoxaemia were observed in all dogs in the study. Clinically increased CFT, decreased MAP and CVP, haematologically decreased WBC and platelet counts, increased PCV, decreased pH and HCO_3 values, increased base deficit, biochemically decreased total protein concentration and increased Na concentration were observed during endotoxaemia (Table 1). Body temperature generally decreased from base line to 4 h in the ISS group but significantly increased in the HSS group. The HR was higher at 30 min and 2 h in the HSS group than in the ISS group. The RR started to decrease at 2 h in the ISS and HSS groups, and at 75 min in the HSS + LRS and HSS + SBS groups. Within the HSS groups, CFT started to significantly increase from 75 min in the HSS + LRS and HSS + SBS groups. After treatment onset, MAP markedly increased in all groups except the ISS group. After initiation of treatment, CVP increased from the endotoxaemia until 4 h in all groups (Table 2).

PCV and Hg values were similar to each other in all groups (Table 3). PCV and Hg values continuously increased in the ISS and HSS groups, but decreased especially from 75 min in the HSS + LRS and HSS + SBS groups. Plasma volume decreased during endotoxaemia and continously increased significantly in all groups except the ISS group. Decreasing WBC and platelet counts during endotoxaemia continued to the end of the study in all groups.

Table 1. The results of clinical, haematological and biochemical examinations from baseline at endotoxaemia in all dogs.

Parameter	Baseline $X \pm S_x$	Endotoxaemia $X \pm S_x$	Reference Value*
T/C	38.2 ± 0.9	37.8 ± 1.8***	37.5-39.3
HR/bpm	74.2 ± 13.4	96.3 ± 13.3***	70-140
RR/bpm	16.6 ± 6.2	29.7 ± 10.2***	10-30
CFT/s	1.5 ± 0.5	3.5 ± 0.6***	1-2
MAP/mmHg	104.2 ± 15.9	56.8 ± 5.2***	90-110
CVP/mmHg	6.4 ± 1.5	0.7 ± 0.4***	0-10
WBC/mm^3	8450 ± 3316	1535 ± 852***	6000-17000
PCV(%)	37.1 ± 2.6	44.3 ± 5.9***	37-55
Hg/g/dl	12.3 ± 1.1	14.9-1.9***	12-18
PLT x $10^3/mm^3$	243.6 ± 119.7	43.0 ± 20.4***	200-900
Plasma volume(%)	100 ± 0.0	75.4 ± 15.3***	100
pH	7.3 ± 0.04	7.1 ± 0.07***	7.31
pCO_2/mmHg	36.3 ± 5.09	51.3 ± 7.24***	29-42
BE/mEq/L	-4.33 ± 7.0	-9.32 ± 4.9**	0 ± 4
HCO_3/ mEq/L	22.3 ± 3.08	17.0 ± 3.6***	18-24
tCO_2/mmHg	23.2 ± 5.9	19.6 ± 5.49***	25 ± 4
TP/g/dl	7.4 ± 1.0	6.1 ± 1.1***	5.4-71
Na/mEq/l	133.6 ± 10.9	137.5 ± 10.5**	140-155
Cl/mEq/l	104.5 ± 4.8	109 ± 6.6**	105-115

**$p < 0.01$ ***$p < 0.001$ * Kirk, Bistner, Ford (1998): The handbook of small animal practise.

Table 2. The results of clinical examination in all groups.

Parameter	group	baseline $X \pm S_X$	E. toxaemia $X \pm S_X$	10 min $X \pm S_X$	30 min $X \pm S_X$	75 min $X \pm S_X$	2 h $X \pm S_X$	4 h $X \pm S_X$
	ISS	38.2 ± 0.9	37.9 ± 2.1	37.6 ± 2.3	37.2 ± 1.9	36.7 ± 1.8	36.7 ± 0.8	36.9 ± 0.1^{A}
T	HSS	38.1 ± 0.8	37.2 ± 2.1	37.3 ± 3.0	37.2 ± 1.9	37.0 ± 1.2	37.1 ± 0.4	37.0 ± 0.1^{B}
(°C)	HSS + LRS	38.5 ± 0.8	37.1 ± 1.8	37.2 ± 2.1	37.2 ± 2.1	37.5 ± 2.5	37.7 ± 3.0	38.4 ± 0.2^{B}
	HSS + SBS	38.0 ± 1.2	37.9 ± 1.1	37.6 ± 1.1	37.7 ± 0.4	37.9 ± 1.0	38.0 ± 0.9	$38.1 \pm 0.5^{B*}$
	ISS	82 ± 11.0	90 ± 10.3	107.6 ± 21	112.4 ± 4.2^{A}	114 ± 28.2	120 ± 8.7^{A}	140 ± 12.1
HR	HSS	78 ± 16.4	103.7 ± 10	105 ± 36.3	106 ± 2.6^{B}	124 ± 5.6	138 ± 25.4^{B}	134 ± 19.8
bpm	HSS + LRS	67.6 ± 17.3	95.3 ± 11.9	97 ± 16.0	101 ± 1.3^{AB}	107.6 ± 9.7	108 ± 12.4^{A}	105 ± 15.9
	HSS + SBS	70.6 ± 5.7	98.6 ± 20.1	108 ± 26.0	104 ± 2.1^{AB}	119 ± 19.0	113 ± 11^{AB}	119 ± 19.0
	ISS	13.6 ± 2.4^{a}	27.5 ± 11.6^{b}	26.5 ± 17.5^{b}	27.0 ± 18.2^{b}	28.3 ± 19^{b}	30.0 ± 6.5^{ab}	28.6 ± 6.1^{ab}
RR	HSS	12.6 ± 2.1^{a}	22.0 ± 4.2^{b}	22.0 ± 7.2^{ab}	23.0 ± 15.5^{ab}	27.0 ± 15.5^{b}	18.0 ± 2.8^{ab}	$14.0 \pm 0.0^{ab*}$
bpm	HSS + LRS	12.1 ± 2.5^{a}	33.1 ± 6.8^{b}	25.3 ± 7^{b}	27.8 ± 11.2^{b}	25.6 ± 8^{b}	25.6 ± 13^{b}	$18 \pm 10.9^{b*}$
	HSS + SBS	21.3 ± 10.2	35.3 ± 12.0	22.0 ± 13.1	28.6 ± 8.0	25.6 ± 11.7	24.6 ± 5.0	22.0 ± 0.0
	ISS	1.8 ± 0.4^{a}	3.5 ± 0.8^{b}	3.5 ± 0.8^{bA}	4.0 ± 0.6^{bcA}	4.0 ± 0.7^{bc}	4.3 ± 0.5^{bc}	$5.0 \pm 1.0^{***}$
CFT	HSS	1.6 ± 0.5^{a}	3.2 ± 0.4^{b}	2.8 ± 0.8^{abB}	2.5 ± 0.5^{bB}	2.7 ± 0.5^{b}	3.0 ± 0.0^{b}	2.7 ± 0.5^{b}
(s)	HSS + LRS	1.3 ± 0.5^{a}	3.1 ± 0.4^{b}	2.5 ± 1.0^{abB}	3.3 ± 1.3^{bAB}	3.1 ± 1.5^{b}	3.5 ± 1.3^{b}	$3.4 \pm 1.8^{b*}$
	HSS + SBS	1.0 ± 0.0^{a}	4.0 ± 0.8^{ab}	$2.7 \pm 0.5^{abAB*}$	$3.5 \pm 1.7^{abAB*}$	3.2 ± 1.8^{ab}	4.2 ± 2.6^{b}	$4.5 \pm 3.1^{b*}$
	ISS	96.6 ± 12.1^{a}	53.3 ± 6.0^{b}	53.8 ± 11.5^{bA}	47.0 ± 10.6^{bA}	43.6 ± 8.2^{bA}	43.6 ± 14^{bA}	$47.3 \pm 7^{b***A}$
MAP	HSS	101.0 ± 14.3^{a}	58.6 ± 4.9^{b}	80.8 ± 12.7^{cB}	80.7 ± 13^{acB}	81.3 ± 16^{acB}	80.0 ± 14^{aB}	$87 \pm 21^{a***B}$
mmHg	HSS + LRS	114 ± 18.0^{a}	60.0 ± 0.0^{b}	71.1 ± 13^{abB}	68.1 ± 16^{abB}abB	70.8 ± 19^{abB}	61.5 ± 21^{abB}	$68 \pm 24^{ab***B}$
	HSS + SBS	105 ± 17.3^{a}	55.0 ± 5.7^{b}	$68 \pm 14^{abAB*}$	$58 \pm 20^{abAB**}$	$65.5 \pm 23^{abB*}$	$70.5 \pm 34^{abB*}$	$65 \pm 36^{ab*B**}$
	ISS	5.5 ± 1.5^{c}	0.5 ± 1.5^{a}	12.5 ± 2.5^{bA}	10.5 ± 1.5^{b}	8.5 ± 3.5^{b}	7.0 ± 3.5^{bc}	$6.5 \pm 3.5^{bc***}$
CVP	HSS	7.5 ± 0.5^{b}	1.5 ± 0.5^{a}	8.0 ± 1.5^{bB}	8.5 ± 1.5^{b}	8.0 ± 2.5^{b}	7.0 ± 1.5^{b}	$7.5 \pm 0.5^{b**}$
mmHg	HSS + LRS	6.5 ± 1.5^{b}	-1.5 ± 1.0^{a}	7.5 ± 0.5^{bB}	8.0 ± 2.0^{b}	12.0 ± 4.5^{b}	11.5 ± 3.5^{b}	$10.0 \pm 2.5^{b*}$
	HSS + SBS	6.5 ± 2.0^{b}	1.0 ± 0.5^{a}	$8.5 \pm 0.5^{bB**}$	8.0 ± 2.5^{b}	8.5 ± 1.5^{b}	8.0 ± 2.5^{b}	$7.0 \pm 3.5^{b**}$

*p < 0.005 **p < 0.01 ***p < 0.001

a, b, c: Differences betweeen the values involving different letters on the same line are significant.

A, B: Differences between the values involving different letters on the same line are significant.

Mean pH values were prone to decrease continuosly from initiation of the treatment until the 4 h in the ISS group when compared to the HSS groups. Mean pH value started to increase from 75 min in the HSS + LRS and HSS + SBS groups. Mean PCO_2 values started to decrease from endotoxaemia with the beginning of the treatment, increased from 75 min in the ISS group and 2 h in the other groups. Base deficit increased continuosly in the ISS group but decreased from 75 min in the HSS + LRS and HSS + SBS groups. Mean HCO^-_3 values increased from 30 min in the HSS group, and from 75 min in the HSS + LRS and HSS + SBS groups. Although the changes of tCO_2 and HCO^-_3 values were similar to each other, the tCO_2 value was within normal limits at the end of the study in the HSS + SBS group (Table 4).

Total protein concentrations continued to decrease until 2 h in the ISS and HSS groups, 4 h in the HSS + LRS group, and 75 min in the HSS + SBS group. Sodium concentrations continiued to decrease from 10 min in the ISS, HSS and HSS + LRS groups (Table 5).

Table 3. The results of haematological examinations in all groups.

Parameter	group	baseline $X \pm S_X$	E. toxaemia $X \pm S_X$	10 min $X \pm S_X$	30 min $X \pm S_X$	75 min $X \pm S_X$	2 h $X \pm S_X$	4 h $X \pm S_X$
PCV (%)	ISS	37.1 ± 0.7^{a}	42.3 ± 3.4^{b}	50.6 ± 10.7^{A}	57.3 ± 10.7^{bA}	57.2 ± 10.1^{bA}	55.9 ± 5.1^{bA}	$55.7 \pm 5^{b***A}$
	HSS	36.1 ± 4.8^{a}	44.5 ± 6.4^{b}	43.0 ± 11^{bAB}	46.8 ± 15^{bAB}	48.4 ± 14^{bAB}	50.5 ± 10^{bAB}	$52.6 \pm 7^{b*AB}$
	HSS + LRS	37.8 ± 2.5^{a}	44.2 ± 5.9^{b}	39.2 ± 4.6^{abB}	43.0 ± 4.6^{bB}	39.4 ± 3.1^{abB}	41.0 ± 3.4^{bB}	$39.7 \pm 2^{ab**B}$
	HSS + SBS	37.6 ± 2.7	47.4 ± 8.8	$43.4 \pm 7.1^{AB*}$	$44.1 \pm 6.0^{B**}$	$43.7 \pm 8.0^{B**}$	$48.0 \pm 13^{AB*}$	$45.9 \pm 8^{AB**}$
Hg g/dl	ISS	12.5 ± 0.5^{a}	14.3 ± 1.6^{ab}	16.4 ± 2.9^{bc}	18.5 ± 2.8^{cA}	17.4 ± 3.6^{cA}	18.0 ± 1.6^{c}	$17.7 \pm 1.1^{c**A}$
	HSS	12.1 ± 1.6^{a}	15.1 ± 1.8^{ab}	14.5 ± 3.5^{ab}	14.5 ± 5^{abAB}	15.3 ± 4^{abAB}	16.7 ± 2.1^{ab}	$17.2 \pm 1^{ab*AB}$
	HSS + LRS	12.2 ± 1.7^{a}	14.8 ± 1.8^{b}	13.6 ± 1.9^{ab}	13.6 ± 1.3^{abB}	13.4 ± 1.5^{abB}	14.0 ± 1.8^{b}	$13.0 \pm 1.1^{ab*B}$
	HSS + SBS	12.6 ± 0.7	15.7 ± 2.8	14.3 ± 2.2	14.7 ± 1	$14.5 \pm 2.8^{AB*}$	15.7 ± 4.0	$15.0 \pm 3.2^{AB*}$
WBC x 10^3/mm^3	ISS	8.5 ± 4.3^{a}	1.6 ± 0.9^{b}	1.3 ± 0.9^{b}	1.0 ± 0.6^{b}	2.1 ± 1.4^{b}	2.8 ± 1.2^{b}	$3.6 \pm 1.6^{b***}$
	HSS	6.7 ± 2.0^{a}	1.8 ± 0.5^{b}	1.5 ± 0.8^{b}	1.7 ± 0.4^{b}	2.2 ± 0.2^{bc}	2.3 ± 0.1^{bc}	$4.4 \pm 0.6^{c***}$
	HSS + LRS	9.0 ± 3.5^{a}	1.0 ± 0.8^{b}	1.2 ± 0.8^{b}	1.7 ± 1.1^{b}	2.0 ± 1.4^{b}	2.2 ± 1.5^{b}	$3.2 \pm 2.8^{b***}$
	HSS + SBS	9.6 ± 3.3^{a}	1.7 ± 1.0^{b}	1.9 ± 0.2^{b}	1.5 ± 0.4^{b}	1.0 ± 0.3^{b}	2.0 ± 1.2^{b}	$3.1 \pm 1.0^{b*}$
PLT x 10^3/mm^3	ISS	236 ± 15^{a}	54 ± 16^{b}	63 ± 11^{b}	66 ± 11^{b}	87 ± 14^{b}	118 ± 18^{b}	$125 \pm 15^{b*}$
	HSS	162 ± 14^{a}	28 ± 2^{b}	61 ± 12^{bc}	97 ± 43^{bc}	120 ± 38^{ac}	119 ± 37^{ac}	$133 \pm 57^{ac**}$
	HSS + LRS	318 ± 10^{a}	36 ± 2^{b}	124 ± 6^{bc}	131 ± 6^{bc}	164 ± 8^{c}	163 ± 7^{c}	$163 \pm 8^{c***}$
	HSS + SBS	243 ± 10^{a}	54 ± 8^{b}	82 ± 4^{b}	104 ± 4^{b}	111 ± 6^{b}	109 ± 7^{b}	$110 \pm 11^{b**}$
Plasma Volume (%)	ISS	100.0 ± 0.0^{a}	82.0 ± 10.0^{bA}	62.6 ± 19.9^{cA}	48.5 ± 15.9^{cA}	46.6 ± 15.3^{cA}	47.9 ± 9.8^{cA}	$48.8 \pm 8^{c***A}$
	HSS	100.0 ± 0.0^{a}	69.7 ± 18.0^{bB}	74.7 ± 3^{acAB}	85.1 ± 1.3^{acB}	76 ± 33^{abcAB}	68 ± 21^{abcAB}	$62.6 \pm 3^{abc*AB}$
	HSS + LRS	100.0 ± 0.0^{a}	76.8 ± 17^{bAB}	93.5 ± 17^{acB}	79.8 ± 10^{bcB}	90.5 ± 13^{abcB}	85.7 ± 17^{abcB}	$95.9 \pm 6^{abc*B}$
	HSS + SBS	100.0 ± 0.0^{a}	$75.4 \pm 5^{bAB*}$	$89.4 \pm 3^{abAB*}$	$86 \pm 10^{abAB*}$	$88.6 \pm 13^{abB**}$	$78.9 \pm 14^{bB*}$	$74 \pm 21^{b*AB*}$

*$p < 0.005$ **$p < 0.01$ ***$p < 0.001$

a, b, c: Differences betweeen the values involving different letters on the same line are significant.

A, B: Differences between the values involving different letters on the same line are significant.

Throughout the study, 3 dogs died at 25, 50 and 60 min in the ISS group, and 2 dogs died at 45 and 90 min in the HSS group, respectively. After the monitoring periods, all dogs were re-animated and hospitalised, as needed. Water was provided *ad libitum*, and a standardised pelleted diet was fed daily at 9:00 pm and 5:00 pm until complete recovery.

Discussion

In this study, the criteria of endotoxaemia were observed within 40 min after giving *E. coli* endotoxin via intravenous route to each dog, as reported in previous studies (4-7,14,17). Endotoxaemia is characterised by the typical alterations in clinical and laboratory test results (1,6,10,24,26). In agreement with other studies (5,6,17,26,), clinically decreased body temperature, increased HR and RR, prolonged CFT, decreased MAP and CVP, haematologically decreased WBC and platelet counts and decreased plasma volume, increased PCV and Hg values indicated endotoxaemia in all dogs in the present study. Released vasoactive substance in response to the presence of endotoxin in the bloodstream leads to arterial hypotension and circulatory failure (5-8). In our study, hypotension was characterised by decreased MAP (56.8 ± 5.2 mm Hg) and increased CFT (3.5 ± 0.6 s) during endotoxaemia ($p < 0.001$). Cohen et al. (8) reported that MAP ≤ 60 mm Hg was accepted as typical hypotension after endotoxin administration. In addition to hypotension, decreased CVP may be interpreted as an indicator of hypovolaemia, as well as the pooling of venous blood in the pripheral vasculaturates and spleen.

Haematologically, endotoxaemia is characterised by leukopaenia, neutropaenia (26,27) and thrombocytopaenia (17,24,26-28). In our study, the

Table 4. The results of blood gas analysis in all groups.

Parameter	group	baseline $X \pm S_X$	E. toxaemia $X \pm S_X$	10 min $X \pm S_X$	30 min $X \pm S_X$	75 min $X \pm S_X$	2 h $X \pm S_X$	4 h $X \pm S_X$
pH	ISS	7.3 ± 0.0^{a}	7.1 ± 0.1^{b}	7.1 ± 0.1^{bA}	7.0 ± 0.4^{b}	7.0 ± 0.1^{ab}	7.0 ± 0.1^{ab}	6.9 ± 0.2^{b*}
	HSS	7.3 ± 0.0^{a}	7.1 ± 0.0^{b}	7.1 ± 0.0^{bAB}	7.2 ± 0.0^{ab}	7.1 ± 0.2^{b}	7.0 ± 0.1^{b}	7.1 ± 0.1^{b*}
	HSS + LRS	7.3 ± 0.0^{a}	7.1 ± 0.0^{b}	7.2 ± 0.8^{cB}	7.1 ± 0.8^{ac}	7.2 ± 0.0^{bc}	7.1 ± 0.1^{ac}	7.1 ± 0.1^{bc**}
	HSS + SBS	7.3 ± 0.0^{a}	7.1 ± 0.0^{b}	7.1 ± 0.1^{bAB*}	7.1 ± 0.1^{b}	7.2 ± 0.1^{ab}	7.2 ± 0.0^{ab}	7.2 ± 0.2^{ab*}
pCO_2 mmHg	ISS	36.2 ± 4.5^{ab}	48.2 ± 7.2^{a}	34.8 ± 12.5^{ab}	25.1 ± 3.2^{b}	45.7 ± 2.9^{ab}	39.4 ± 2.0^{ab}	46.5 ± 9.6^{ab*}
	HSS	32.3 ± 6.1^{ab}	52.8 ± 8.4^{b}	38.2 ± 11.0^{a}	27.2 ± 2.3^{a}	35.1 ± 3.9^{ab}	51.3 ± 1.8^{b}	40.0 ± 4.9^{ab*}
	HSS + LRS	37.5 ± 5.5^{a}	53.9 ± 7.8^{b}	47.0 ± 9.6^{a}	43.7 ± 6.5^{a}	38.8 ± 4.6^{a}	44.6 ± 4.6^{ab}	34.6 ± 9.9^{a*}
	HSS + SBS	38.8 ± 2.9^{a}	48.3 ± 0.2^{b}	41.1 ± 14.3^{ab}	39.7 ± 4.6^{ab}	30.1 ± 14.8^{ab}	40.5 ± 8.9^{ab}	43.2 ± 9.3^{b*}
BE mEq/L	ISS	-3.8 ± 1.2^{a}	-10.1 ± 4.5^{b}	-15.9 ± 4.2^{bc}	-15.8 ± 3.0^{bc}	-16.3 ± 3^{bcA}	-17.0 ± 4.0^{bc}	-19.3 ± 6.0^{c***}
	HSS	-4.5 ± 1.2^{a}	-10.7 ± 1.8^{b}	-12.3 ± 3.1^{b}	-10.4 ± 2.1^{b}	-13.2 ± 4^{bAB}	-10.8 ± 0.0^{b}	-9.5 ± 0.1^{b*}
	HSS + LRS	-0.4 ± 2.4^{a}	-7.4 ± 1.0^{b}	-10.6 ± 5.4^{b}	-12.1 ± 7.4^{b}	-11.7 ± 5^{bAB}	-11.1 ± 7.0^{b}	-11.4 ± 8.4^{b*}
	HSS + SBS	-3.1 ± 2.3^{a}	-9.4 ± 2.3^{ab}	-13.8 ± 2.5^{b}	-11.9 ± 5.3^{ab}	-7.3 ± 2.9^{abB*}	-8.0 ± 4.1^{ab}	-10.2 ± 5.8^{ab*}
HCO_3 mEq/L	ISS	21.9 ± 4.1^{a}	16.4 ± 4.3^{b}	13.0 ± 2.6^{b}	13.1 ± 1.7^{b}	12.9 ± 1.9^{bA}	12.3 ± 2.4^{b}	11.3 ± 3.3^{b***}
	HSS	20.4 ± 2.1^{a}	16.1 ± 1.0^{b}	14.7 ± 2.8^{b}	16.4 ± 1.2^{b}	14.5 ± 2.8^{bAB}	14.2 ± 2.4^{b}	14.8 ± 3.2^{b*}
	HSS + LRS	24.0 ± 2.3^{a}	18.7 ± 3.7^{b}	16.4 ± 3.9^{b}	15.5 ± 5.0^{b}	16.6 ± 3.6^{bAB}	15.1 ± 4.6^{b}	14.0 ± 5.2^{b**}
	HSS + SBS	22.3 ± 1.8^{a}	17.5 ± 4.4^{ab}	15.7 ± 2.8^{ab}	15.5 ± 3.8^{b}	20.6 ± 2.3^{abB*}	18.9 ± 4.4^{ab}	17.2 ± 4.1^{a*}
tCO_2 mmHg	ISS	23.8 ± 4.9^{a}	19.0 ± 8.3^{ab}	14.6 ± 5.0^{b}	14.7 ± 6.7^{b}	14.0 ± 2.4^{b}	12.6 ± 3.6^{b}	13.0 ± 1.6^{b*A}
	HSS	23.8 ± 2.4^{a}	21.0 ± 4.5^{ab}	18.2 ± 6.1^{ab}	13.6 ± 1.8^{b}	17.9 ± 5.5^{ab}	19.3 ± 0.9^{ab}	19.6 ± 1.0^{ab*AB}
	HSS + LRS	26.6 ± 4.6^{a}	22.0 ± 3.6^{ab}	18.0 ± 5.4^{ab}	17.6 ± 8.5^{ab}	16.2 ± 3.0^{b}	18.2 ± 4.2^{ab}	19.1 ± 2^{ab*AB}
	HSS + SBS	23.4 ± 1.8	22.8 ± 5.6	19.9 ± 6.7	22.1 ± 10.2	26.6 ± 14.0	20.2 ± 2.7	23.9 ± 7.7^{B*}

*p < 0.005 **p < 0.01 ***p < 0.001

a, b, c: Differences betweeen the values involving different letters on the same line are significant.

A, B: Differences between the values involving different letters on the same line are significant.

Table 5. The results of biochemical examinations in all groups.

Parameter	group	baseline $X \pm S_X$	E. toxaemia $X \pm S_X$	10 min $X \pm S_X$	30 min $X \pm S_X$	75 min $X \pm S_X$	2 h $X \pm S_X$	4 h $X \pm S_X$
TP g/dl	ISS	7.3 ± 2.9	6.6 ± 1.5	5.3 ± 4.9	4.9 ± 0.5	6.0 ± 1.0	6.3 ± 1.1	6.8 ± 1.7
	HSS	6.1 ± 1.9	5.9 ± 0.7	5.3 ± 1.0	5.4 ± 0.8	5.5 ± 1.1	5.1 ± 1.5	6.9 ± 0.4
	HSS + LRS	6.9 ± 1.1	6.1 ± 1.2	6.2 ± 1.3	5.9 ± 1.6	5.6 ± 1.5	5.5 ± 1.2	5.5 ± 1.0
	HSS + SBS	6.4 ± 1.6	5.9 ± 1.6	6.4 ± 1.9	6.0 ± 1.4	5.5 ± 1.5	7.0 ± 0.0	6.2 ± 1.5
Na mEq/l	ISS	147 ± 5.2	152.5 ± 7.5	146 ± 4.6	147.0 ± 7.0	153.0 ± 11.5	149.0 ± 2.8	155.5 ± 3.5
	HSS	140.8 ± 11.8	148.6 ± 6.6	145.0 ± 18.6	140.6 ± 21.1	140.1 ± 6.5	140.8 ± 15.4	140.4 ± 10.5
	HSS + LRS	146.4 ± 11.8	147.0 ± 15.1	142.3 ± 9.2	143.0 ± 12.0	142.0 ± 12.0	146.4 ± 16.9	141.5 ± 11.2
	HSS + SBS	141.5 ± 12.0	141.0 ± 1.4	140.0 ± 5.6	137.0 ± 10.3	132.0V10.6	144.0 ± 1.3	138.0 ± 1.4
Cl mEq/l	ISS	105.7 ± 7.6	108.2 ± 13^{A}	109.5 ± 8.18	100.7 ± 13.0	104.2 ± 6.8	115.7 ± 15.9	118.0 ± 21.1
	HSS	104.6 ± 17.2	109.3 ± 12^{AB}	119.6 ± 10.5	117.6 ± 15.3	103.7 ± 9.7	107.0 ± 10.2	118.5 ± 18.5
	HSS + LRS	102.5 ± 10.2	110.6 ± 1.1^{B}	119.3 ± 15.7	118.2 ± 25.4	108.8 ± 9.4	106.9 ± 24.5	104.9 ± 15.5
	HSS + SBS	127.0 ± 4.2	129.0V1.4^{B*}	131.5 ± 2.1	125.0 ± 1.4	124.5 ± 0.7	125.0 ± 4.5	128.0 ± 1.2

*p < 0.005

A, B: Differences between the values involving different letters on the same line are significant.

causes of leukopaenia and thrombocytopaenia might be related to the chemotactic effects of mediators and bone marrow depression associated with the endotoxin. This is supported by the study of Tsuchiya et al. (24), who determined that the control of platelet activating factor (PAF) production, PAF-induced effects, or both may be important in the treatment of dogs with Gram-negative bacterial infections and associated thrombocytopaenia and neutropaenia. Many vascular beds are dilated, but some are constricted, resulting in the maldistribution of blood flow during endotoxaemia (2,29). Microvascular thrombosis caused by the aggregation of neutrophiles and platelets leads to tissue and cellular hypoxia (2,3,14,30). In the present study, as indicators of circulatory failure and haemaconcentration, PCV and Hg values increased, and tough plasma volume and total protein concentration decreased from base line. Despite clinical and haematological proof of dehydration, total protein concentration decreased during endotoxaemia. This may be attributed to the loss of protein-rich plasma into the extravascular spaces from the intravascular spaces, as noted in other studies (14,30,31).

In addition to the minimum data base of haemotocrit and total protein, blood gas analysis is frequently used to determine the imbalances of acid/base status and to prepare the most effective treatment plan in patients in intensive care units (2,3,10). Metabolic acidosis is the result of an accumulation of metabolic waste-products, and lack of buffer systems during endotoxaemia (7,10). In the study, decreased pH, increased base deficit and increased PCO_2 values during endotoxaemia were indicators of metabolic acidosis in dogs.

Successful long-term outcomes depend on therapeutic regimens. Most regimens emphasise the importance of administering fluids such as isotonic or hypertonic crystalloids and colloids early during shock therapy to increase vascular volume, cardiac output and improve tissue perfusion (10,13,17,18,21,32). Therefore, ISS, HSS, HSS + LRS and HSS + SBS were used in the management of endotoxaemia in the study.

Decreased body temperature during endotoxaemia in all groups was considered an indicator of hypodynamic shock stage characterised by hypothermia ($p < 0.001$). After initiation of the treatment, body temperature increased in the HSS + LRS and HSS + SBS groups ($p < 0.05$), and continuously decreased in the ISS group. This result shows the efficiency of fluids given to improve impaired functions. This is in agreement with Schertel et al. (18), who reported that decreased body temperature at the shock stage returned to normal limits in the HSS group, and continued to decrease in the ISS group.

The HR increases in response to endotoxaemia (6,20,26,30). In the present study, the HR incresed from base line until endotoxaemia but remained within normal limits ($p < 0.001$). This is probably due to bradyarrhythmia, a side effect of xylazine HCl (9). Heart and respiratory rates increased at 10 min in all groups. This is most likely due to the short half-life of xylazine HCl, as well as the minimal effect of isoflouran on HR and RR (33,34). The side effects of HSS such as bradyarrhythmia and haemolysis were not observed due to the the application of the recommended dose and infusion rate of HSS. HR and RR were higher in the ISS groups than in the HSS groups. This probably occurred due to myocardial contractility was increased by the HSS, and that ISS was inadequate in treating metabolic abnormalities (21,29,34). This is in agreement with another study (33) which reported that patients treated by small volumes of HSS improved better than those given large volumes of ISS. The beneficial haemodynamic and pulmonary effects of HSS may be attributed to the activity of hypertonic solution on the cardiovascular system producing an arteriolar vasodilatation, a direct positive cardiac inotropic effect and a fluid shift resulting in plasma expansion.

CFT, MAP, PCV, total protein and plasma volume as well as blood gases are of importance for the evaluation of circulatory function during endotoxaemia (18,25,32). CFT increased in the ISS group but decreased in the others. This may be related to the beneficial effects of HSS such as the production of precapillary dilatation and high osmalarity, as well as increased cardiac output and myocardial contractility. This is supported by the fact that volume replacement with artificial colloids yielded haemodynamic stability and adequate tissue oxygen supply, whereas the administration of crystalloid alone jeopardised tissue perfusion and oxygenation (35). The reason for the continuous increase of CFT in the ISS group ($p < 0.001$) is most likely due to the disadvantages of ISS, including haemodilution, increasing hydrostatic pressure and short-half life in plasma. This conclusion is supported by increased PCV, Hgb and CVP ($p < 0.01$), as well as decreased MAP and plasma volume ($p < 0.001$) in the ISS group. The reason for increased CFT ($p < 0.05$)

and decreased CVP from 75 min in the HSS + LRS and HSS + SBS groups may be due to the short half-life of the haemodynamic effects of crystalloid solutions.

As with clinical and haematological alterations, arterial pH value continuously decreased in the ISS group, and increased to near normal limits in the HSS groups. In contrast to the HSS groups, increased pCO_2, tCO_2 and BE, and decreased HCO^-_3 values were determined in the ISS group, suggesting that metabolic acidosis would be effectively treated by use of HSS. This conclusion may be explained by the beneficial effects of HSS on cardiovascular function such as the reduction of systemic vasculary resistance, and the increase of plasma volume and cardiac output (21,29,34,36). pH, pCO_2, HCO^-_3, tCO_2 and BE values in the HSS + LRS and HSS + SBS groups were better than in the other groups. This probably occurred after the administration of small amounts of LRS or SBS.

Altough Na and Cl concentrations in the HSS groups were higher than in the ISS group, electrolyte values never reached limits in the LRS and SBS groups. The reason for this may be that isotonic crystalloid solutions (LRS and SBS) are not effectively used to treat electrolyte deficit, as reported in previous studies (19,23). This result in the study is supported by another study (18) demonstrating that Na and Cl values in dogs with shock, treated by LRS, were not statistically different between pre- and post-treatment. Kellum et al. (23) also reported that serum Cl concentrations were increased by saline influsion, but Na concentrations did not change.

On the basis of the results of this study, ISS was not considered effective. In addition, 3 dogs in the ISS and 2 dogs in the HSS group died at different times. Measured parameters in the HSS + LRS and HSS + SBS groups were better than in the other groups. In conclusion, HSS (7.2%) + SBS (1.3%) was the most effective therapy in the management of dogs with experimentally induced endotoxaemia.

References

1. Parillo, J.E.: Pathogenic mechanism of septic shock, N. Engl. J. Med., 1993; 328: 1471-1477.
2. Weeren, F.R., Muir III, W.W.: Clinical aspects of septic shock and comprehensive approaches to treatment in dogs and cats, J. Am. Vet. Med. Assoc., 1992; 200 (12): 1859-1870.
3. Goodwin, J.K., Schaer, M.: Septic shock, Vet. Clin. N. Am. Small Anim. Prac., 1989; 19 (6): 1239-1258.
4. Frangogiannis, N.G., Mendoza, L.H., Smith, C.H., Michael, L.H., Entman, M.L.: Induction on the synthesis of the C- X-C chemokine interferon gamma inducible protein-10 in experimental canine endotoxernia. Cell Tissue Res., 2000; 302 (3): 365- 376.
5. Belloma, R., Kellum, J.A., Gandhi, J.R., Pinsky, M.R., Ondulik, B.: The effects of intensive plasma water exchange by filtration on hemodynamics and soluble mediators in canine endotoxaemia. Am. J. Respir. Crit. Care. Med., 2000; 16 (5): 1429-1436.
6. Pinsky, M.R., Rico, P.: Cardiac contractility is not depressed in early canine endotoxic shock. Am. J. Respir. Crit. Care. Med., 2000; 161 (4): 1087 -1093.
7. Hayes, J.K., Luo, X., Wong, K.C., Mccames, S., Tseng, C.K.: Effects of dobutamine, norepinephrine and epinephrine or intramucosal pH and hemodynamics of dogs during endotoxic shock. Acta Anaesthesiol. Scn., 1998, 36 (3): 113-126.
8. Cohen, R.I., Huberfeld, S., Genovese, J., Steinberg, H.N., Scarf, S.M.: A comparison between the acute effects of nitric oxide synthase inhibition and fluid resuscitation on myocardial function and metabolism in endotoxemic shock. J. Crit. Care., 1996; 11(1): 27-36.
9. Barragry, T.B.: Veterinary Drug Therapy, Lea & Febiger, Philadelphia, 1994; 185-189.
10. Haskins, S.C.: Management of septic shock, J. Am. Vet. Med. Assoc., 1992; 200 (12): 1915-1924.
11. Kirby, R.: Shock: Aggressive resuscitation procedures, W.S.A.V.A. XVII World Cong., 1992, Rome, 609-610.
12. Garvey, M.S.: Fluid and electrolyte balance in critical patients, Vet. Clin. N. Am. Small. Anim. Prac., 1989; 19 (6): 1021-1057.
13. Zhong, J., Rubin, J.L., Parker, J.L., Edams, H.R.: Cardiodynamic response to *Escherichia coli* endotoxaemia: effects of fluid resuscitation. Shock, 1994; 2 (3): 203- 209.
14. Hardie, E.M.: Life-threatening bacterial infection, Comp. Cont. Edu., 1995; 17 (6): 763-777.
15. Strombeck, D.R., Guilford, W.G.: Small Animal Gastroentorology, 2nd edition, Wolfe Publishing Ltd., California, 1991; 328-330.
16. W olfsheimer, K.J.: Fluid therapy in the critically ill patient. Vet. Clin. N. Am. Small Anim. Prac., 1989; 19 (2): 361-379.
17. Batmaz, H: Effects of isotonic, hypertonic and hypertonic + isotonic sodium chloride solutions in dogs with endotoxemia. U. Ü. Vet. Fak. Derg., 1996; (1-2-3) 15: 113-127.
18. Schertel, E.R., Allen, D.A., Muir, W.W., Hansen, B.D.: Evaluation of a hypertonic sodium chloride/dextran solution for treatment of traumatic shock in dogs, J. Am. Vet. Med. Assoc., 1996; 208 (3): 366-370.

19. Ajito, T., Suziki, K., Iwabuchi, S.: Effects of intravenous infusion of a 7.2% hypertonic saline solution on serum electrolytes and osmotic pressure in healthy beagles J. Vet. Med. Sci., 1999; 61 (6): 637-641.

20. Haskins, S.C.: Shock, Handbook of Veterinary Procedures Emergency Treatment, W.B. Saunders Comp., Philadelphia, 1990; 33-52.

21. Ing, R.D., Nazeeri, M.N., Zeldes, S., Dulchavasky, S.A., Diebel, L.N., Scholten, D.: Hypertonic saline/dextran improves septic myocardial performance. Am Surg., 1994; 60 (7): 505-508.

22. Kellum, J.A., Rico, P., Garuba, A.K., Pinsky, M.R.: Accuracy of mucosal pH and mucosal arterial carbon dioxide tension for detecting mesenteric hypoperfusion in acute canine endotoxaemia. Crit. Care Med., 2000; 28 (2): 462-466.

23. Kellum, J.A., Bellomo, R., Kramer, D.J., Pinsky, M.R.: Etiology of metabolic acidosis during saline resuscitation in endotoxemia. Shock, 1998; 9 (5): 364-368.

24. Tsuchiya, R., Kyatoni, K., Scott, M.A, Nishizon, K., Ashida, Y., Mochizuki, T., Kitao, S., Yamada, T., Kobayashi K.: Role of platelet activating factor in development of thrombocytopenia and neutropenia in dogs with endotoxemia. Am. J. Vet. Res., 1999; 60 (2): 216-221.

25. Fantoni, D. T., Auner Junior, J.O., Futema, F., Cortopassi, S.R., Migliati, E.R., Faustino, M., De Oliveria, C.M. : Intravenous administration of hypertonic sodium chloride solution with dextran or isotonic sodium chloride solution for treatment of septic shock secondary to pyometra in dogs. J. Am. Vet. Med. Assoc., 1999; 215 (99): 128-1287.

26. Yılmaz, Z.: The effects of dobutamine, methylprednisolone, flunixin meglumine and enalapril in the treatment of dogs with experimentally induced septic shock, U. Ü. Vet. Fak. Derg., 2000; 19 (1-2): 1- 7.

27. Brown, M.R., Rogers, K.S.: Neutropenia in dogs and cats. A retrospective study of 261 cases. J. Am. Anim. Hosh. Assoc., 2001; 37 (2): 131-139.

28. Bush B.M.: Interpretation of Laboratory Results for Small Animal Clinicians, Blackwell Scientific Publications, London, 1991; 31-330.

29. Luypeart, P., Vincent, J.L., Domb, M., Linden, P.V., Blecic, S., Azimi, G., Bernard, A.: Fluid resusitation with hypertonic saline in endotoxic shock. Circ. Shock, 1986; 20: 311-320.

30. Green, E.M., Adarns, H.R.: New perspectives in circulatory shock: Pathophysiologic mediators of the mammalian response to endotoxaemia and sepsis, J. Am. Vet. Med. Assoc., 1992; 200 (12): 1834-1841

31. Arnold, P., Suter, P.F., Hagen, A.: New aspects of therapy in hypovolemic and septic shock in small animals, Kleintierpraxis, 1995; 40: 321-329.

32. Sing, S., Annig, P.B., Winlove, C.P., Evans, T.W.: Regional transcapillary albumin exchange in rodent endotoxaemia: effects of fluid resuscitation and inhibition of nitric oxide synthase. Clin. Sci. (Colch), 2001; 100 (1): 81-89.

33. Dupe, R., Bywater, R.J., Goddard, M.: A hypertonic infusion in the treatment of experimental shock in calves and clinical shock in dogs and cats, Vet. Rec., 1993; 133: 585-590.

34. Duval, D.: Use of hypertonic saline solutions in hypovolemic shock. Comp. Cont. Edu., 1995; 17 (10): 1228-1231.

35. Funk, W., Baldinger, V.: Microcirculatory perfusion during volume therapy: a comparative study using crystalloid or colloid in awake animals. Anesthesiology, 1995; 82 (4): 975-982.

36. Constable, P.D., Schmall, L.M., Muir III, W.W.: Respiratory, renal, hematologic and serum biochemical effects of hypertonic saline solution in endotoxemic calves, Shock, 1991; 52 (7): 990-998.