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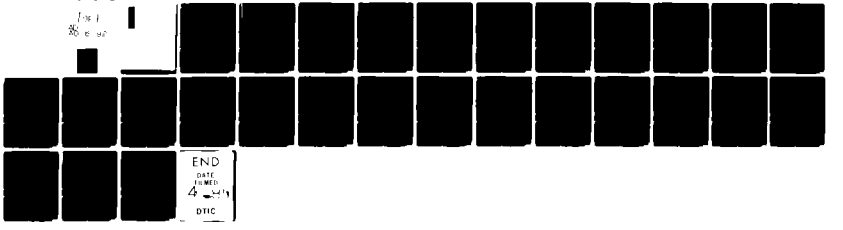

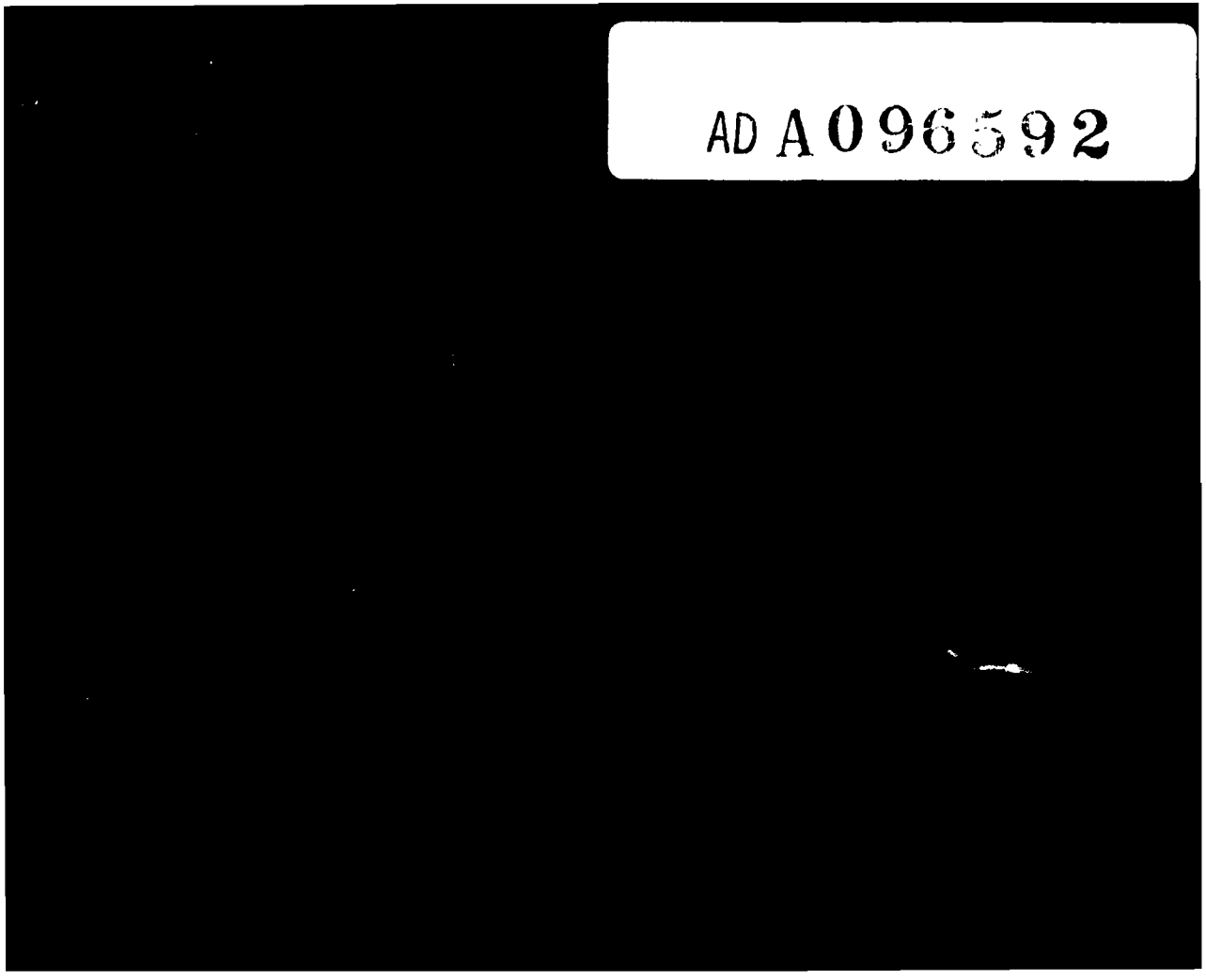

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Task No. NR 207-207

TECHNICAL REPORT NO. 142

SURVIVAL OF PRIMATES IN LETHAL SEPTIC SHOCK FOLLOWING DELAYED TREATMENT WITH STEROID

L. B. Hinshaw, L. T. Archer, B. K. Beller-Todd,

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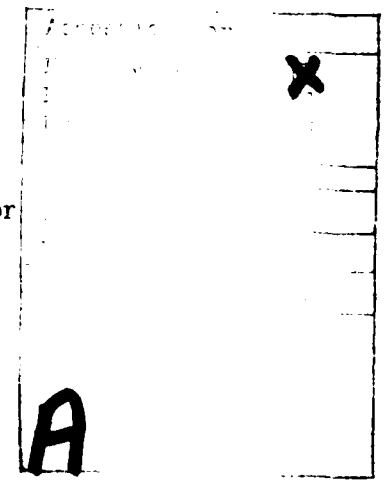
Prepared for Publication

in

Circulatory Shock

Veterans Administration Medical Center and Departments of Physiology and Biophysics, Surgery, Pathology, and Microbiology/Immunology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma 73104

26 February 1981



ABSTRACT

We recently developed a methylprednisolone sodium succinate (MPSS)/ gentamicin sulfate (GS) regimen that prevented death in baboons given a 2-hour infusion of LD_{100} E. coli (J. Surg. Res. 28:151, 1980). Steroid treatment was begun in that study 30 minutes after initiation of E. coli. Our current aim was to determine if baboons would survive if MPSS treatment was delayed until all E. coli were infused and severe hypotension had ensued. Fourteen lightly anesthetized baboons (Papio c. cynocephalus) were administered E. coli and seven were then treated with MPSS and GS for 10 hours. All nontreated baboons died while 6 of 7 treated animals survived. In the treated group, hypoglycemia and hypoinsulinemia were reversed, tachycardia was reduced and neutrophil recovery was improved. Baboons with delayed MPSS, however, evidenced diminished perfusion and recovered slower than those with earlier MPSS treatment. In conclusion, primates in septic shock are clearly protected with delayed steroid/antibiotic therapy.

KEY WORDS: septic shock, steroid therapy, antibiotic therapy, baboon, E. coli infusion, methylprednisolone sodium succinate (MPSS), gentamicin sulfate (GS), endotoxin shock, hypoglycemia, hypoinsulinemia, neutrophil recovery

INTRODUCTION

There has been a recent acceleration of interest in the combined use of steroids and antibiotics in the treatment of experimental and clinical septic shock (1-6). Recent findings from this laboratory have shown that dogs subjected to 100% lethal intravenous infusions of E. coli are completely protected against the typical pathophysiologic and lethal actions of E. coli by multiple sustaining infusions of both methylprednisolone sodium succinate and gentamicin sulfate (3). However, either agent, administered by itself without the other, offers no protection to the animal. These findings have also been reported in the baboon subjected to E. coli shock (6), and its responses to treatment with the steroid and antibiotic were very similar to those of the dog (3); that is, all baboons receiving both agents were permanent healthy survivors. In the baboon experiments (6), infusion of methylprednisolone sodium succinate was initiated after 25% of the E. coli organisms had been administered, while gentamicin sulfate infusion was delayed until all organisms had been introduced into the blood.

The question has arisen as to a possible loss of therapeutic effectiveness if the administration of steroid were to be delayed. The purpose of the present study was to determine if baboons would survive a 2-hour lethal E. coli infusion if steroid treatment was delayed until all E. coli were infused, at which time animals would have experienced severe systemic hypotension. The baboon was chosen as a test animal because of its phylogenetic proximity to man, and the delay in steroid treatment was selected to achieve closer relevance to the timing of treatment in humans. In this present report, comparisons have been made between baboons administered E. coli alone with those receiving steroid treatment 2 hours after the initiation of E. coli infusion. Findings clearly support the

effectiveness of steroid treatment but suggest that certain adverse effects of shock may not be readily prevented or reversed if steroid administration is delayed.

MATERIALS AND METHODS

The present study utilized 14 adult baboons of the subspecies, Papio c. cynocephalus. The baboons were allowed a stabilization period of 1 to 2 months in the local animal facility, then were fasted for 24 hours and given water ad libitum prior to experimentation. On the day of the study they were first immobilized with ketamine hydrochloride, 14 mg/kg, intramuscularly, and then slowly intravenously anesthetized with sodium pentobarbital via a percutaneous catheter positioned in the cephalic vein. The radial or femoral artery and femoral or brachial vein were exposed aseptically and cannulated for pressure measurements and blood sampling, and for infusions of live organisms, 0.9% NaCl, and methylprednisolone sodium succinate (MPSS) and gentamicin sulfate (GS). Each baboon was placed on its side with controlled-temperature heating pads positioned above and beneath the body and a temperature probe placed in the rectum. A tracheal cannula was orally inserted and periodic positive pressures were applied hourly to prevent atelectasis. An equilibration period of one hour was allowed each animal before beginning the E. coli infusion. Each baboon was provided with saline administration, 4 to 6 ml/kg/hr, to maintain hydration requirements and to prevent hemoconcentration during the 12-hour monitoring period.

Baboons of either sex were divided into two groups and each administered a 2-hour infusion of live E. coli: the control group (N=7; average weight, 17 kg) received an average of 2.4 (± 0.2)$\times 10^{10}$ organisms/kg body weight prepared as previously described (3, 6, 7). The experimental group (N=7;

average weight, 15 kg) received approximately $3.1(\pm 0.3)x10^{10}$ E. coli/kg body weight, and the steroid methylprednisolone sodium succinate (MPSS; The Upjohn Company, Kalamazoo, MI) and the antibiotic gentamicin sulfate (GS; Schering Pharmaceutical Corporation, Kenilworth, NJ), as described in the protocol (Table I). The steroid and antibiotic were administered only after all live organisms had been infused. Maintenance infusions of MPSS and GS were then given at levels providing optimal plasma concentrations (3, 6). A total of 18 mg/kg of GS and 75 mg/kg of MPSS was infused during a [illegible]-hour period following the administration of live E. coli. GS was additionally injected intramuscularly at 12 hours and twice daily for 3 days, during which time animals were maintained in the recovery room and observed until death for a minimum of 7 days, indicating permanent survival. Most animals were arbitrarily euthanized at a later period (8 - 71 days).

Blood pressure and heart rate were monitored on a Sanborn recorder. Arterial blood samples were taken for determinations of glucose, insulin, lactate, white blood cell and differential leukocyte concentrations, platelets, pH, pCO_2, pO_2, blood urea nitrogen, endogenous creatinine, serum gentamicin, and blood concentrations of viable E. coli, as previously reported (3, 6).

Statistics were carried out utilizing the Student's t test for paired and unpaired data and the Fisher's Exact Test for survival data.

RESULTS

The effects of methylprednisolone sodium succinate (MPSS) and gentamicin sulfate (GS) in the baboon following a 2-hour infusion of E. coli were studied during a 12-hour period of continuous monitoring, followed by an extended observation period, with 7 days selected as the minimum

time for designation of animals as "permanent survivors". Table II provides data for survival times: all baboons in the control group, given E. coli alone, died within 42 hours (mean 17 hours). Animals treated with MPSS and GS responded favorably to treatment; five baboons were permanent survivors while one died at 15 hours and one (#2) at 6 days. Baboon #2, at autopsy, showed signs of severely diminished blood flow to the forelimb in which the femoral artery had been ligated for arterial pressure measurements. Survival rates of treated animals (5 of 7 or 6 of 7) are statistically significant (Fisher's Exact Test analysis). During recovery, four of the permanent survivors developed dermal ulcerations on the pelvic, hind limb and gluteal areas, and on the tail, in one instance. These ulcerations were treated by the veterinarian using Septisol wash, hydrogen peroxide, and Panolog ointment, and healed within two weeks.

Changes in E. coli blood concentrations are shown in each of the two groups in Table III. Each baboon's blood culture was negative at zero time. Five minutes after completion of organism infusion, blood concentrations were similar in both groups (approximately 10^7 organisms per ml blood). At 4 hours following onset of organism infusion, the concentration of organisms in the treated group was less than the control group, approximately 10% of the latter ($p<0.02$), while during the remainder of the study, significant differences in concentrations between the groups were not seen. Mean values were, however, lower at 12 hours in animals receiving MPSS and GS (10^2 versus 10^3 organisms per ml blood).

Mean serum concentrations of gentamicin sulfate in the seven treated animals were 19.1 (±1.5), 13.1 (±1.2), and 13.7 (±1.4) µg/ml at 3.5, 8.5, and 12 hours, respectively.

Mean systemic arterial pressure and heart rate changes are illustrated in Figure 1. Blood pressure responses to E. coli were similar in both treated and nontreated baboons and could not be used as a prognosis for survival unless they were obviously low (see animal #2, upper frame of Figure 1). Heart rate changes, on the other hand, were generally of prognostic value inasmuch as rates were significantly lower in animals receiving steroid and antibiotic ($p<0.05$).

Figure 2 portrays changes in blood glucose and serum insulin concentrations in treated and nontreated baboons. Animals receiving E. coli only, without MPSS and GS, became progressively hypoglycemic and hypoinsulinemic during the 12-hour observation period. In contrast, treated animals maintained glucose levels within the normal range and insulin concentrations were elevated above the control, nontreated group.

Marked reductions in numbers of white blood cells and mature neutrophils were seen during the first 4 hours in all baboons of both treated and nontreated groups (Figure 3). However, from 4 to 12 hours after the onset of E. coli infusion, numbers of these cell types and immature neutrophils progressively increased in animals receiving MPSS and GS infusions compared with the nontreated animals. Of note was the observation of thrombocytopenia in all animals of both groups after E. coli administration with no differences between treated and nontreated baboons at any time during the 12-hour period.

There were no significant differences in pO_2, pH, pCO_2 and lactate between baboons receiving E. coli alone and those administered MPSS and GS following delivery of the total E. coli dose (Figure 4). The figure shows that pCO_2 progressively fell, and lactate rose in both groups while pH remained relatively constant during the observation period. No significant

changes in pO_2 were seen in either group when values during shock were compared with those at zero time.

Figure 5 demonstrates small but significant ($p<0.05$) rises in blood urea nitrogen (BUN) concentrations in both treated and untreated animals, while those receiving MPSS and GS showed lesser elevations at 8 and 12 hours. Mean increases in endogenous creatinine concentrations were mild in both groups.

Rates of saline administration were similar in the two groups: an average of 5.5 and 7.4 ml per kg per hour were infused during the 12-hour period in nontreated and treated baboons, respectively. These quantities were not significantly different ($p>0.05$). Hematocrit changes were insignificantly different between the treated and untreated groups ($p>0.05$): mean values at control (zero time) were 45 and 43, and at 12 hours were 46 and 40, respectively, in nontreated and treated baboons.

DISCUSSION

Our recent reports have shown that the lethal pathophysiology of E. coli-induced shock is effectively prevented by combined glucocorticoid and antibiotic therapy in both dogs (3) and nonhuman primates (6). We demonstrated in a recent report (6) that baboons administered LD_{100} E. coli are effectively treated by infusions of methylprednisolone sodium succinate (MPSS) administered after one-fourth of the organisms were given, followed by subsequent infusions of MPSS and gentamicin sulfate (GS) during a 12-hour period. All animals thus treated were healthy permanent survivors (6). Although a massive number of organisms had been administered ($7x10^9$ organisms/kg body weight) prior to MPSS infusion in that study, aortic pressure had not yet fallen to the lowest point it would have had treatment not been initiated (6). The present study was designed to extend this work in baboons by delaying steroid treatment until all organisms were given

($2\text{-}3\times10^{10}$ E. coli/kg), thus allowing the early maximum drop in mean aortic pressure to occur prior to commencing steroid treatment. This delay of onset of treatment also provided a closer alignment of the baboon model with the clinical situation. Results demonstrate the remarkable effectiveness of methylprednisolone sodium succinate and gentamicin sulfate even when their administration is withheld until all organisms have been given. However, in delaying the initiation of the MPSS, several obstacles were uncovered: recovery of normal eating and physical activities was delayed, body surface ulcers developed in some animals, and the survival rate was slightly decreased.

Evidence for the beneficial effects of MPSS, even when its initial administration is delayed until all organisms have been given and the animals have demonstrated a maximal fall in blood pressure, is as follows: glucose and insulin concentrations are maintained at near normal values, tachycardia is blunted, augmentation of mature and immature neutrophil numbers is seen, and survival is remarkably improved.

Fluid administration was not considered a prominent factor in the effective resuscitation inasmuch as E. coli-shocked dogs treated similarly with MPSS and GS, but receiving no fluid support, were permanent survivors (3).

Findings have consistently shown that steroid administration alone is ineffective in the treatment of E. coli shock in both dogs (3) and primates (6, 9, 10). It is essential that steroid and antibiotic are given concomitantly. Our recent reports suggest that large doses of MPSS do not depress phagocytic activity in baboon blood (8) or delay time of recovery of the animal (3, 6). No evidence was obtained to support the view that gentamicin sulfate adversely affected the kidneys: BUN and serum creatinine concentrations increased as much or more in baboons given E. coli alone without GS as

those who were fully treated with MPSS and GS. A previous study in baboons showed that BUN and creatinine concentrations completely returned to control values during the recovery period (6), and the only animals demonstrating the presence of urine flow were those receiving MPSS plus GS (6).

Proposed mechanisms of protection of MPSS and GS infusions against the pathophysiologic effects of E. coli in the baboons of the present study have been suggested in a previous report (6) and include improvement of hemodynamic, metabolic, endocrinologic and phagocytic functions resulting in the maintenance of normal morphologic-functional status of tissues including brain, liver, heart, kidneys and adrenals (6).

Emphasis on the baboon has been pursued because of its phylogenetic proximity to man, which extends the application of findings in this species to the human patient in sepsis or septic shock.

ACKNOWLEDGMENTS

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TABLE I

TREATMENT REGIMEN IN BABOONS SUBJECTED TO ESCHERICHIA COLI-INDUCED SHOCK

Group	N	Agent Administered	Dosage, E. coli/kg*	Time after onset of E. coli infusion	Duration and route of administration
E. coli only		E. coli organisms	$2.4(\pm 0.2)\times 10^{10}$	Zero time (0)	0-120 min, IV
E. coli + MPSS + GS	7	E. coli organisms	$3.1(\pm 0.3)\times 10^{10}$	Zero time (0)	0-120 min, IV
		MPSS[†]	30 mg/kg	+125 min	15 min, IV
		GS[§]	9 mg/kg	+130 min	60 min, IV
		MPSS	15 mg/kg	+150 min	120 min, IV
		GS	4.5 mg/kg	+365 min	30 min, IV
		MPSS	15 mg/kg	+365 min	120 min, IV
		GS	4.5 mg/kg	+9 hr	30 min, IV
		MPSS	15 mg/kg	+10 hr	120 min, IV
		GS	4.5 mg/kg	+12 hr	IM
		GS	4.5 mg/kg	Twice daily, 3 days	IM

Saline infusions are substituted for drugs in the E. coli only group.

*Both groups, volume infused, 2.1 ml/kg

[†]Methylprednisolone sodium succinate

[§]Gentamicin sulfate

TABLE II

SURVIVAL DATA IN BABOONS RECEIVING ESCHERICHIA COLI ORGANISMS AND TREATED WITH METHYLPREDNISOLONE SODIUM SUCCINATE AND GENTAMICIN SULFATE*

Group	Baboon Number	Sex	Weight (kg)	Survival Time
E. coli only	1	F	15.8	10.5 hr
	2	F	16.2	3 hr
	3	M	19.1	5 hr
	4	M	19.0	32 hr
	5	M	18.2	42 hr
	6	M	16.0	12.5 hr
	7	M	15.5	16 hr
Mean			17.6	17 hr
E. coli + MPSS + GS	1	M	13.0	6 months†
	2	F	16.0	6 days
	3	F	18.0	53 days§
	4	M	13.0	8 days§
	5	F	14.1	71 days§
	6	M	17.5	36 days§
	7	F	13.4	15 hours
Mean			15.0	

*The difference in survival between the groups assessed by the Fisher Exact Test is significant ($p<0.05$).

†Permanent residence supplied by private party.

§Euthanized.

TABLE III

ESCHERICHIA COLI BLOOD CONCENTRATIONS* IN BABOONS SUBJECTED TO LD_{100} ESCHERICHIA COLI SHOCK AND TREATED WITH STEROID AND ANTIBIOTIC

Group		Mean number organisms infused per kg body weight	Zero time	+125 min	+4 hr	+6 hr	+12 hr
E. coli only	Mean	2.4×10^{10}	Negative	8.1×10^{6}	2.9×10^{3}	1.3×10^{3}	1.2×10^{3}
	SE(±)	0.2×10^{10}		2.7×10^{6}	1.0×10^{3}	0.4×10^{3}	0.5×10^{3}
	N†	7	7	7	6	5	4
E. coli + MPSS + GS	Mean	3.1×10^{10}	Negative	1.2×10^{7}	2.7×10^{2}	3.7×10^{2}	3.3×10^{2}
	SE(±)	0.3×10^{10}		0.8×10^{7}	1.0×10^{2}	1.9×10^{2}	2.2×10^{2}
	N	7	7	7	7	7	7
	p§	<0.05			<0.02		

*Number of organisms/ml blood.

†Number of baboons.

§Unpaired analysis comparing groups.

FIGURE LEGENDS

Figure 1. Individual changes in mean systemic arterial pressure and mean heart rate (±SE) in baboons receiving E. coli alone and those with E. coli followed by intermittent infusions of methylprednisolone sodium succinate (MPSS) and gentamicin sulfate (GS). MPSS and GS were infused only following total administration of E. coli as described in Table I.

= $p<0.05$, paired comparison within group with zero time value.

= $p<0.05$, unpaired comparison between groups at designated times.

Figure 2. Changes in serum insulin and blood glucose concentrations in treated and nontreated baboons; mean (±SE). Each group, N=7.

= $p<0.05$, paired comparison within group with zero time value.

= $p<0.05$, unpaired comparison between groups at designated times.

Figure 3. Changes in white blood cell, mature and immature neutrophils, and platelets in baboons receiving E. coli alone versus those receiving E. coli and subsequently treated with MPSS and GS.

= $p<0.05$, paired comparison within group with zero time value.

= $p<0.05$, unpaired comparison between groups at designated times.

N = number above each bar.

Figure 4. Alterations of pH, pCO_2 and lactate in baboons receiving E. coli alone (N=7) and E. coli plus subsequent infusions of MPSS and GS (N=7).

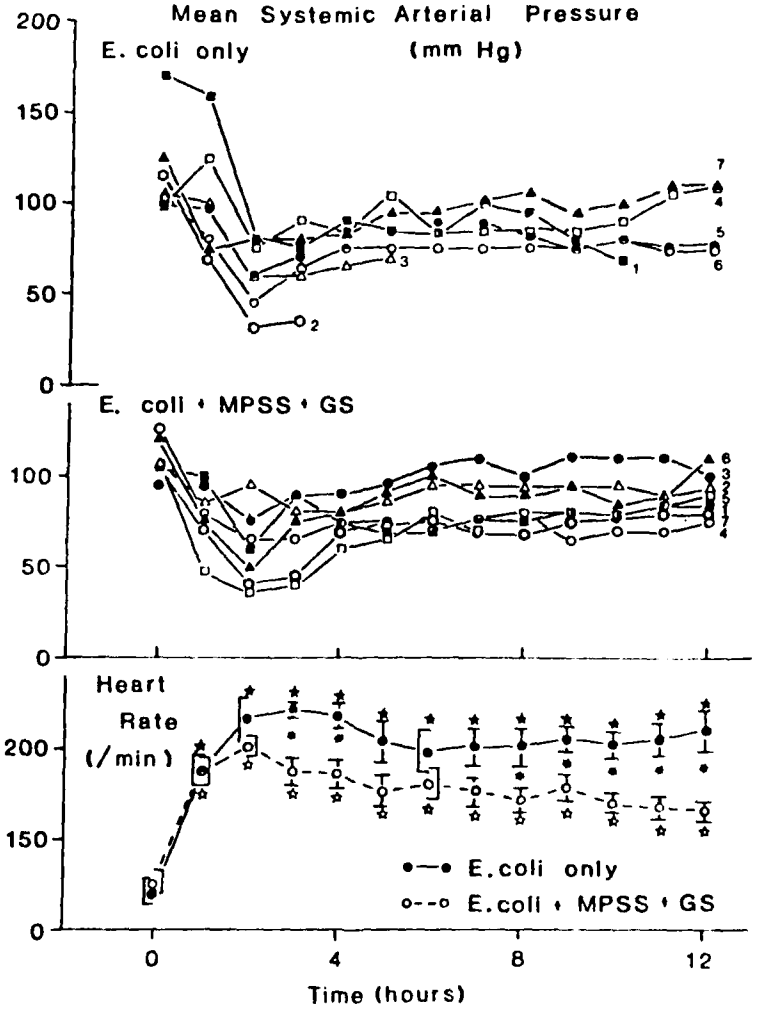
= $p<0.05$, paired comparison within group with zero time value.

= $p<0.05$, unpaired comparison between groups at designated times.

Figure 5. Changes in blood urea nitrogen (BUN) and endogenous creatinine concentrations in treated (N=7) and nontreated baboons (N=7).

= $p<0.05$, paired comparison within group with zero time value.

= $p<0.05$, unpaired comparison between groups at designated times.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E. coli only
E. coli + MPSS + GS
Heart Rate (/min)
E.coli only
E.coli + MPSS + GS
Time (hours)
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100
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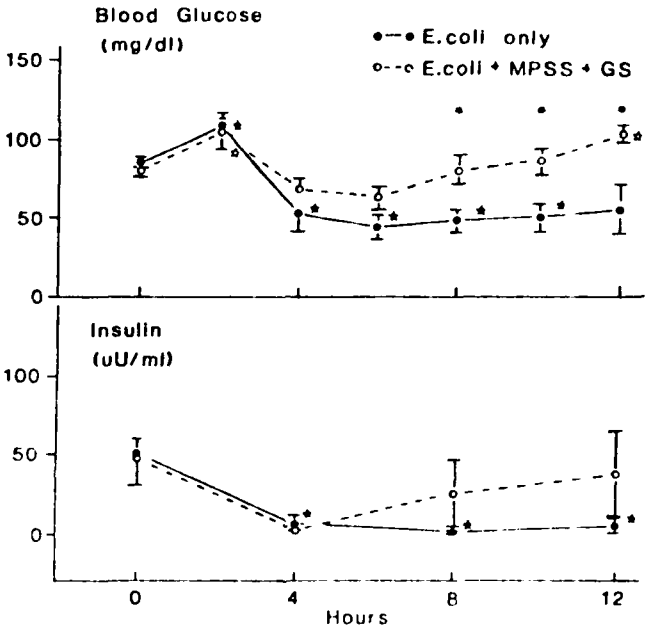
0
0
4
8
12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100
50
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Insulin
(uU/ml)
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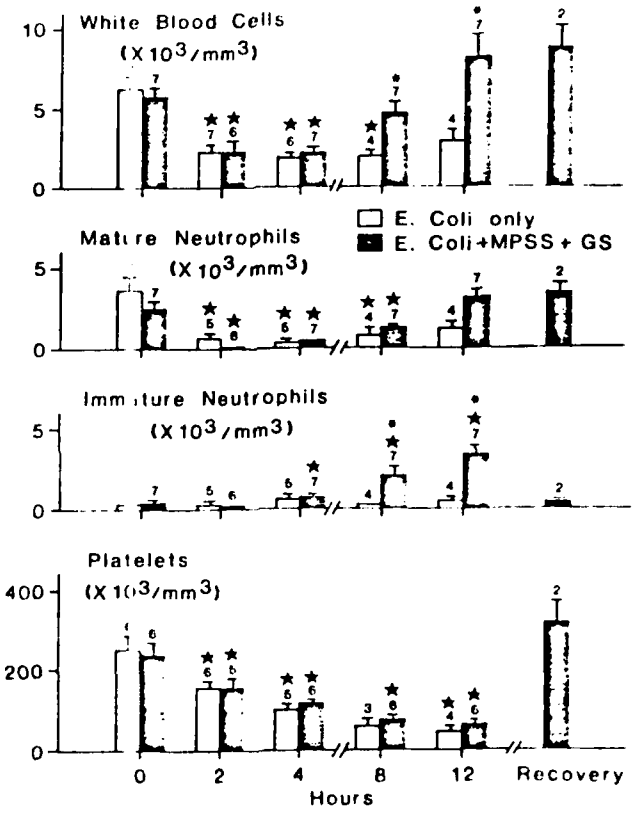
50
0
0
4
8
12
Hours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10
5
0
E. Coli only
E. Coli+MPSS + GS
Mature Neutrophils
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5
0
Immature Neutrophils
(X 10³/mm³)
5
0
Platelets
(X 10³/mm³)
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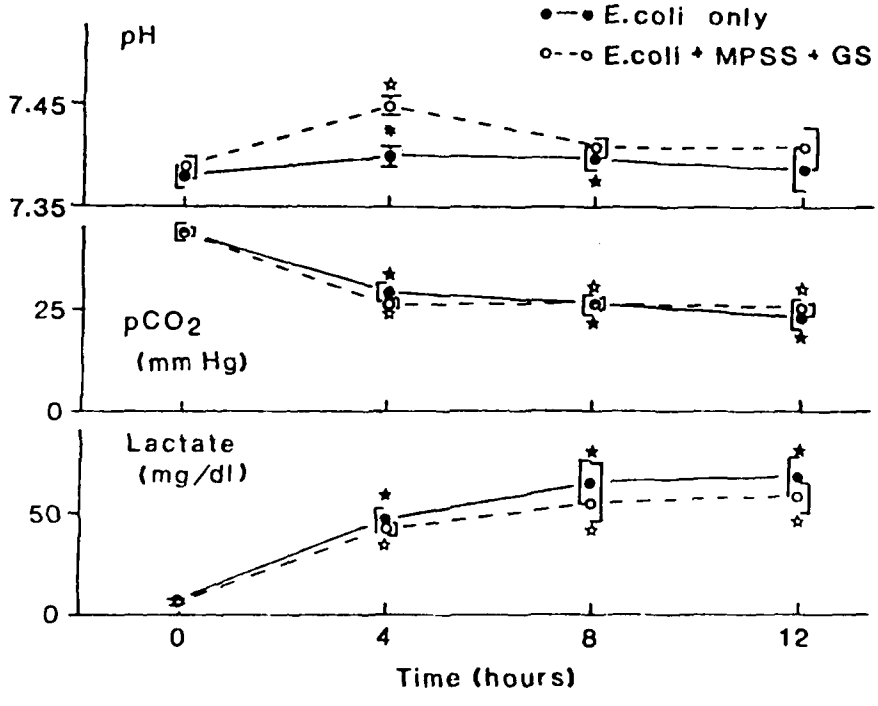
0
2
4
8
12
Recovery
Hours


E.coli only
E.coli + MPSS + GS
pH
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Lactate
(mg/dl)
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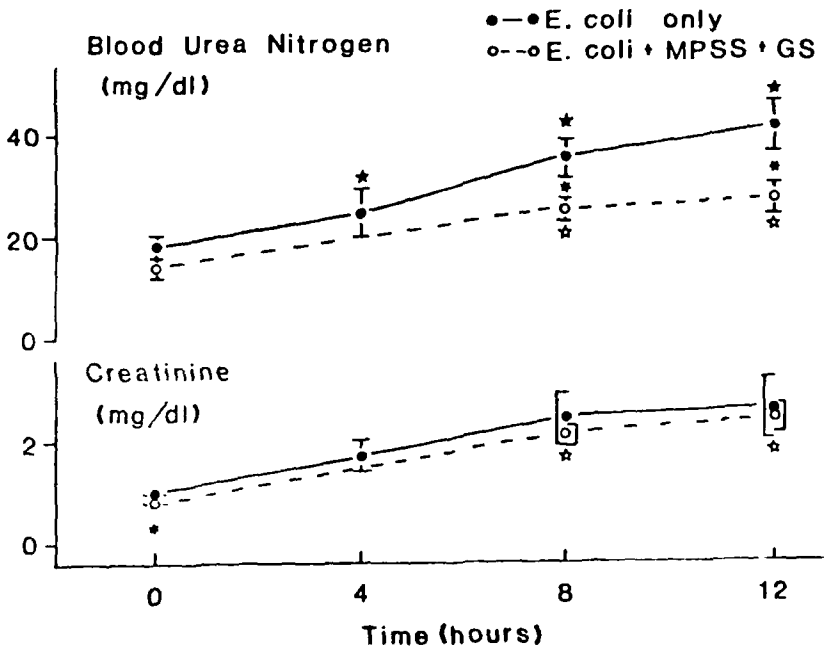
0
0
4
8
12
Time (hours)


●—●E. coli only
o--oE. coli + MPSS + GS
Blood Urea Nitrogen
(mg/dl)
40
20
0
Creatinine
(mg/dl)
2
0
0
4
8
12
Time (hours)

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septic shock, steroid therapy, antibiotic therapy, baboon, E. coli infusion, methylprednisolone sodium succinate (MPSS), gentamicin sulfate (GS), endotoxin shock, hypoglycemia, hypoinsulinemia, neutrophil recovery

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We recently developed a methylprednisolone sodium succinate (MPSS)/gentamicin sulfate (GS) regimen that prevented death in baboons given a 2-hour infusion of LD_{100} E. coli (J. Surg. Res. 28:151, 1980). Steroid treatment was begun in that study 30 minutes after initiation of E. coli. Our current aim was to determine if baboons would survive if MPSS treatment was delayed until all E. coli were infused and severe hypotension had ensued. Fourteen lightly anesthetized baboons (Papio c. cynocephalus) were administered E. coli and →

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