

The Effect Of Piracetam On Liver Damage In Dogs Submitted To Hemorrhagic Shock

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Citation

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Abstract

Background: To investigate the effect of piracetam on liver damage in dogs submitted to hemorrhagic shock. **Methods:** The subjects were randomized into four subgroups each consisting of 10 dogs. Hemorrhagic shock was caused in Group I for 1 hour and no treatment was given to this group. Blood and saline solutions were administered to Group II following 1 hour hemorrhagic shock. Blood and piracetam were given to Group III following 1 hour shock. No shock was caused and no treatment was applied to Group IV. Blood samples were obtained at the onset of the experiment at 60, 120 and 180 minutes for lactate, arterial blood gases, bicarbonate, aspartate transaminase and alanine transaminase analysis. For histopathological examination, liver tissue samples were obtained at the end of the experiment. **Results:** It was observed that the improvement in lactate, aspartate transaminase and alanine transaminase levels in Group III was more than Group II. It was seen that the recovery in liver damage in Group III was greater than control group. **Conclusion:** Piracetam, added to the treatment, may decrease liver damage in hemorrhagic shock.

INTRODUCTION

Despite various recent developments regarding early care of trauma patients, multiple organ failure continues to be a major factor for morbidity and mortality occurring after the resuscitation of the hemorrhagic shock.¹ The progressive hepatic disorder presenting after the hemorrhagia plays a significant role in the development of multiple organ disorder. Despite acute aggressive treatment, experimental studies have shown a persistence of the reduction in microvascular blood flow which causes hypoperfusion and progressive hepatic damage.²

The primary aim in the treatment of hemorrhagic shock is to improve the circulating blood flow.³ In hemorrhagic shock, while volume therapy can improve macrohemodynamics and maintain the systemic oxygen distribution, it falls short of correcting the disrupted microcirculation.¹³ During the treatment of hemorrhagic shock, additional pharmacological agents which could improve microcirculation and reverse hepatic toxicity may be required.¹

Piracetam is the first nootropic agent which is shown to have cytoprotective, antihypoxic, and antioxidant properties

alongside improving microcirculation.⁴ By including piracetam in the treatment regimen of hemorrhagic shock, we targeted to elucidate if it could improve the disorder in the hepatic microcirculation and hepatic damage causing multiple organ failure.

The aim of the present study was to investigate the influence of piracetam on the reduction of the hepatic damage displayed by dogs following subjection to hemorrhagic shock.

MATERIALS AND METHODS

The present experimental study was realized with the support of the Erciyes University Research Fund and carried out in Hakan Cetinkaya Experimental and Clinical Research Center (DEKAM) laboratories, Emergency Medicine Department, Medical Faculty, Erciyes University, following the achievement of the approval from the Ethics Committee (Project No: TT- 03-17). Forty male mongrel dogs weighing between 17-32 kg were employed in the study. The dogs were not fed during the 12 hours prior to the study.

Anesthesia was achieved by the administration of 5mg / kg Ketamine (Ketalar®, Pfizer) + 1mg / kg Xylazine

Hydrochloride (Rompun®, Bayer) through a catheter placed into the left foreleg vein. Dogs were left for spontaneous respiration without intubation. Surgical sterilization rules were applied during the trial. The femoral artery and vein of the dogs were spotted and a polyethylene catheter with 3mm diameter was placed into both of them. One route of the 3-way stop cock inserted to the end of the artery was connected to the monitor through the pressure transducer in order to obtain a continuous measurement of the arterial pressure. The other route was used for inflicting hemorrhage and drawing blood for analyzing lactate and blood gas. In shock, several prognostic parameters are employed which indicate if the treatment is applied properly or not. In the present study, in order to measure the severity of the hemorrhagic shock and the efficiency of the treatment, we used blood lactate and base deficit parameters which reflect tissue perfusion best in hemorrhagic shock. The catheter placed into the vein was used for administering blood, saline, and piracetam.

Hemorrhage in the subjects submitted to shock was induced by a catheter placed into the artery according to modified Wiggers technique with the bleeding rate of 50cc/m until a mean arterial pressure of 40mmHg was achieved. In order to maintain the arterial pressure of the subjects included in the shock-applied groups at 40mmHg, either the bleeding was started again or the withdrawn blood was returned. Following the infliction of hemorrhage, the blood of the subjects was stored in phlebotomy bags until the beginning of the reinfusion at room temperature.

The subjects were divided into 4 groups, where each of them consisted of 10 dogs.

1. Shock group (Group I, n=10):

One-hour long shock was applied to the subjects and no treatment was delivered after the shock.

2. Control Group (Group II, n=10):

One-hour long shock was applied to the subjects. Following shock, reinfusion of the blood withdrawn from themselves and administration of 4cc/kg (800mg/kg) IV piracetam were carried out.

3. Piracetam treatment group (Group III, n=10):

One-hour long shock was applied to the subjects. Following shock, the reinfusion of the blood withdrawn from them and the administration of 4cc/kg (800mg/kg) IV piracetam were

carried out.

4. Sham group (Group IV, n=10):

No shock or treatment was applied to the subjects. However, the other procedures were carried out.

Blood samples were obtained for lactate and blood gas analysis from the subjects at 60th, 120th, and 180th minutes.

Laparotomy was carried out on all the subjects through a midline excision at the end of the 3rd hour and a tissue sample was obtained from the liver for histopathologic analysis. All the subjects were sacrificed at the end of the trial by induction of hemorrhage.

ANALYSIS OF BLOOD VALUES

At the beginning of the trial, blood samples were collected from the subjects by a heparinated syringe at 60th, 120th, and 180th minutes. The withdrawn blood samples were analyzed by a Rapid lab 865 autoanalyzer in the Biochemical Laboratory of the Emergency Department. The blood sample obtained for aspartate transaminase (AST) and alanine transaminase (ALT) was analyzed with Tecnicon RA-XT(R) autoanalyzer in the biochemistry laboratory.

HISTOPATHOLOGIC ANALYSIS

Liver tissue samples obtained for histopathologic analysis were fixed in 10% formaline. Following the routine tissue procedures, all the tissues were blocked by paraffin and sections of 5-8µ size were prepared. Staining was carried out with Hematoxylin-eosin and the dyed preparations were evaluated under light microscope. The histopathologic alterations occurring in the liver after the hemorrhagic shock and treatment were evaluated with the system developed by Tsimoyiannis and colleagues (Table 1).⁵

Figure 1

Table 1: Histopathologic evaluation of the liver tissue

Grade	Signs
0	No damage in hepatocytes.
1	Minimal cellular alterations.
2	Only moderate level central lobular damage
3	Serious lobular central damage
4	Moderate central lobular and midzonal damage
5	Serious central lobular and midzonal damage
6	Hepatocytes displaying total destruction

STATISTICAL ANALYSIS

One way ANOVA test was used for comparison of the values of blood pressure, lactate, and blood gas. For Post Hoc evaluation, Scheffe procedure was preferred. Kruskal Wallis variance analysis was applied for the comparison of the results between the groups. Mann Whitney U test was used for the determination of different groups. $p < 0.05$ was recognized as significant.

RESULTS

LACTATE, BASE DEFICIT, BICARBONATE, AND PH VALUES

While blood lactate values were observed to rise during the shock in subjects submitted to hemorrhagic shock, they showed a decrease towards normalization in treated subjects. No statistically significant difference was found between Groups II and III ($p > 0.05$). The difference between Groups II and IV was determined to be statistically significant ($p < 0.05$), whereas the difference between Groups III and IV was not found to be significant ($p > 0.05$). Base deficit values were observed to be increased among hemorrhagic shock groups while they were found to be reduced in the treatment groups. At the end of the trial, the differences between Groups I and II, III, IV were found to be statistically significant ($p < 0.01$). As Groups II, III, and IV were compared with each other, no significant difference was found ($p > 0.05$) (Table II). Bicarbonate values were determined to be reduced in groups subjected to hemorrhagic shock and re-elevated in the treatment groups. At the end of the trial, the differences between Groups I and II, III, IV were found to be statistically significant ($p < 0.01$). As Groups II, III, and IV were compared with each other, no significant difference was found ($p > 0.05$) (Table 2). pH values were observed to have gone low during the hemorrhagic shock. The difference between Groups I and II, III, IV was found to be statistically significant ($p < 0.05$) (Figure 1). As Groups II, III, and IV were compared with each other, no significant difference was found ($p > 0.05$) (Figure 1).

Figure 2

Table 2: Lactate, base deficit, bicarbonate, AST and ALT values among Groups.

	Time (min)	GROUP I X ± SD	GROUP II X ± SD	GROUP III X ± SD	GROUP IV X ± SD	F	P
Lactate (mEq/L)	0	1,9 ± 0,6	2,7±1,3	2,9±1,0	1,9±0,5	3,3	>0,05
	60	7,8 ± 2,3 ^d	7,8±1,5 ^d	8,7± ,4 ^d	2,3±1,1 ^{abc}	31,2	<0,01
	120	8,9 ± 1,7 ^{bcd}	5,2±1,7 ^{ad}	4,3±0,9 ^{ad}	1,7±0,4 ^{abc}	49,8	<0,01
	180	10,2 ± 1,8 ^{bcd}	3,9±1,2 ^{ad}	2,6±0,5 ^a	1,8±0,7 ^{bc}	106,1	<0,01
Base deficit (mmol/L)	0	19,6 ± 2,8	20,5±3,3	23,3±2,6	20,5±3,1	2,9	>0,05
	60	9,7 ± 2,4 ^d	10,8±2,9 ^d	10,2±3,3 ^d	18,7±3,2 ^{abc}	20,3	<0,01
	120	8,2 ± 3,2 ^{abc}	16,2±3,2 ^a	20,0±2,4 ^a	19,6±3,0 ^a	33,9	<0,01
	180	7,1 ± 2,7 ^{abc}	17,1±3,5 ^a	20,7±2,5 ^a	18,1±2,6 ^a	42,7	<0,01
Bicarbonate (mEq/L)	0	6,2 ± 3,1	4,9±2,9	2,5±1,5	4,5±2,1	3,8	>0,05
	60	16,1 ± 3,2 ^d	13,6±3,4 ^d	14,5±3,2 ^d	7,8±4,5 ^{abc}	9,7	<0,01
	120	18,8 ± 4,8 ^{bcd}	8,5±3,0 ^a	5,0±2,6 ^a	6,1±3,3 ^a	31,1	<0,01
	180	21,4 ± 4,5 ^{bcd}	6,5±2,8 ^a	3,8±2,3 ^a	6,7±2,5 ^a	73,7	<0,01
AST (U/L)	0	27,7±8,9	26,0±11,1	27,8±7,2	20,2±8,5	0,12	>0,05
	60	34,6±17,5	29,8±9,1	30,1±8,3	20,2±8,5	0,07	>0,05
	120	47,6±29,0	34,9±17,9	24,6±11,7	20,2±8,5	3,05	<0,05
	180	76,6±47,5 ^{bc,d}	57,4±33,9 ^{ad}	28,2±16,8 ^a	20,2±8,5 ^{ab}	2,58	<0,05
ALT (U/L)	0	30,9±7,2	27,0±5,1	26,8±9,2	21,7±7,8	2,78	>0,05
	60	36,7±12,6	33,6±28,8	34,9±7,2	21,7±7,8	0,07	>0,05
	120	58,6±31,3 ^{bc,d}	31,5±37,7 ^a	18,6±7,0 ^a	21,7±7,8 ^a	5,08	<0,05
	180	79,8±53,9 ^{bc,d}	36,9±19,5 ^{ad}	22,0±11,1 ^a	21,7±7,8 ^{ab}	6,17	<0,05

*Values provide $p < 0.05$ considered as significant.

a: Demonstrate the difference over Group I.

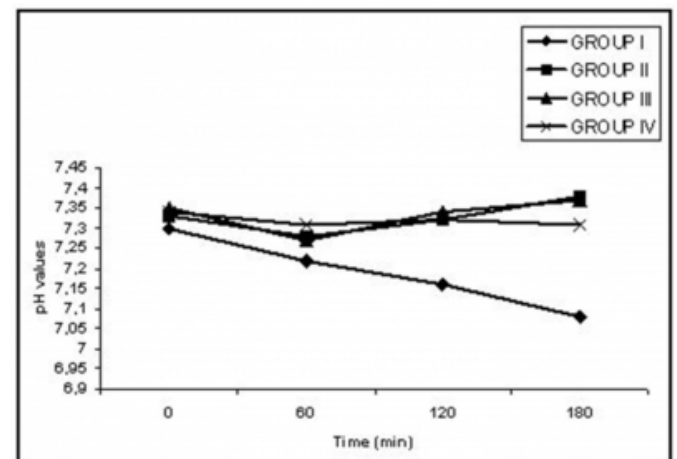
b: Demonstrate the difference over Group II.

c: Demonstrate the difference over Group III

d : Demonstrate the difference over Group IV

Figure 3

Figure 1: pH values among groups



LIVER FUNCTION TESTS

AST and ALT values were found to be elevated during the shock in the groups subjected to hemorrhagic shock. The values were observed to show a drop in the treatment groups. The difference formed between groups II and III was not evaluated to be significant ($p > 0.05$). By 180th minute, a statistically significant difference was found between group

II (the group that was treated with blood and SF) and the sham group ($p < 0.05$). As group III (the group that was treated with blood and piracetam) and sham group were compared, no difference was found ($p > 0.05$) (Table 2).

HISTOPATHOLOGIC EVALUATION

A statistically significant difference was found in the liver tissue between Groups II and IV in terms of histopathologic evaluation ($p < 0.05$). No significant difference was determined between Groups III and IV ($p > 0.05$). The difference between Groups II and III was not statistically significant ($p > 0.05$) (Table 3, 4) (Figure 2, 3).

Figure 4

Table 3: Histopathological Evaluation among Groups

	Group I	Group II	Group III	Group IV	X ²	p
	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)		
Liver	1 (0-4) ^{bcd}	1 (0-2) ^{ad}	0 (0-1) ^a	0 (0-1) ^{ab}	17,0	<0,05

*Values provide $p < 0,05$ considered as significant.
 a: Demonstrate the difference over Group I.
 b: Demonstrate the difference over Group II.
 c: Demonstrate the difference over Group III

Figure 5

Table 4: Histopathological Changes in Liver Tissue

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Group I	1	4	2	2	1	0
Group II	4	5	1	0	0	0
Group III	8	2	0	0	0	0
Group IV	8	2	0	0	0	0

Figure 6

Figure 2: Necrotic cells in liver tissue of a dog in Group II (HE X 200)

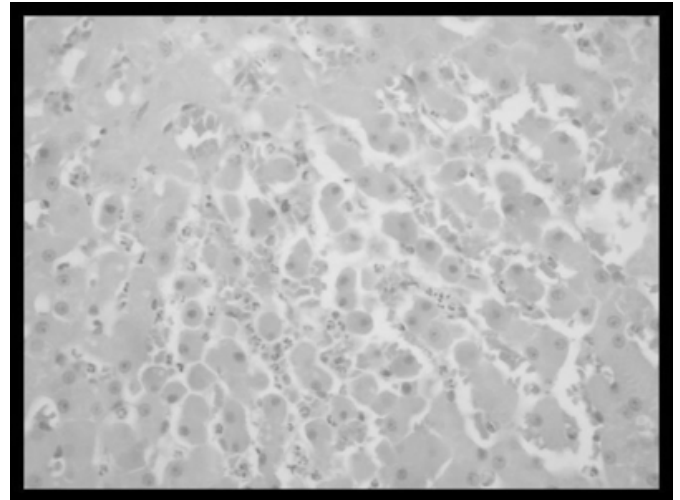
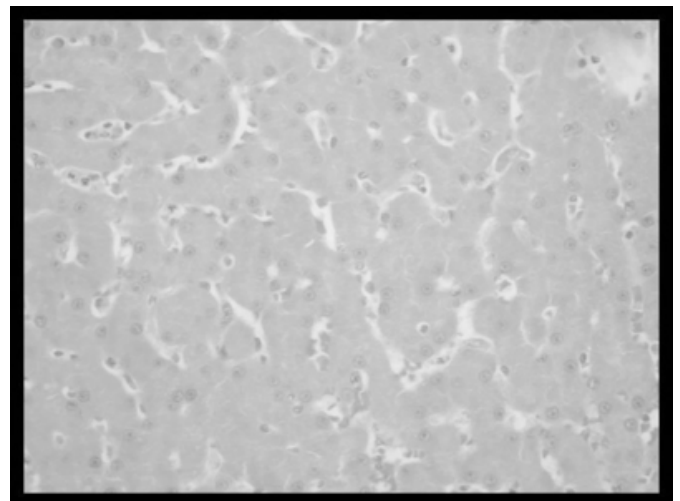


Figure 7

Figure 3: Healing in the liver tissue of a dog after treatment in Group III (HE X 400)



DISCUSSION

In hemorrhagic shock, we witness a disruption in liver blood flow following vasoconstriction formed in splanchnic area during shock, which eventually leads to hepatocellular ischemia. Along the ischemia, the adenosine triphosphate (ATP) levels in hepatocytes drop and pericentral apoptosis occur.² Studies indicate that despite adequate level of resuscitation, liver damage and the hepatic microcirculation failure persist.⁶ While many factors are known to take part in the development of multiple organ failure following hemorrhagic shock and treatment, evidences suggesting a major role of liver dysfunction continue to grow.¹

A progressive study conducted on patients experiencing hemorrhagic shock revealed the mortality rate as 50% and marked multiple organ failure as the most common underlying cause. Liver failure incidence has been found to be over 60% among patients suffering from multiple organ failure.⁶ Following hemorrhagia induced in rats, marked reduction in gastrointestinal perfusion along with a greater damage in liver compared to the other organs have been shown.⁷ While Paxian et al.² showed a rise in tissue ATP levels as a result of fluid therapy in hemorrhagic shock, they found hepatocellular dysfunction as persisting. Wang et al.³ reported a progressive failure of the liver microvascular blood flow after hemorrhagic shock despite adequate level of fluid resuscitation. At the end of the trial, we determined moderate central lobular damage and midzonal damage in the livers of the group subjected to hemorrhagic shock. Consistent with the studies above, the liver damage in the group subjected to administration of blood and placebo SF, was found to persist; we determined grade 1 damage in 5 subjects and grade 2 damage in one subject. As we compared that group with the sham group, the resulting difference was statistically significant.

By considering the possibility of using additional pharmacological agents in order to reduce the amount of liver damage persisting after the hemorrhagic shock and its treatment, we planned to treat the subjects included in our shock model with piracetam and their own blood. Due to its cytoprotective, antihypoxic, and microcirculation-improving effects, we believed that piracetam could benefit the treatment of liver damage associated with shock. In an experimental study performed on rats, piracetam has been found to improve both central and peripheral microcirculation by reducing thrombocyte aggregation and erythrocyte deformability.⁸ Following inducing hypoxia in the in vitro astrocyte cell cultures, Gabryel et al.⁹ applied piracetamin in order to observe its cytoprotective effect and anti-apoptosis influence. In the end, they found a significant reduction in the number of cells exhibiting death or apoptosis as a result of piracetamin application.⁹ Piracetam has been found to be able to prevent changes occurring after hemorrhagia in rats subjected to hypoxia by inducing hemorrhagic shock.¹⁰ Another study showed that piracetam inhibits free radical lipid peroxidation and slows down the oxygen consumption in liver mitochondria.¹¹ Moreover, piracetam has been detected to accelerate aerobic and anaerobic glycolysis and increase ATP concentration.¹² In the present study, we determined a better improvement in the group which received piracetam and blood compared to the

group that received blood and SF. The liver tissue of the subjects who received piracetam in their treatment regime was of similar condition compared to those of sham group subjects. Moreover, the difference between those groups in terms of liver function test results was found not to be statistically significant. The fact that there was no difference between the two groups regarding histopathology and biochemical values suggests that piracetam might reduce the damage occurring in the liver. The comparison sham group and the group subjected to blood and SF revealed no significant difference. This result indicates that applying only blood therapy might not be effective in reduction of the damage occurring in the liver tissue following shock.

There are some parameters in use which show if the treatment is carried out properly or not. Oxygen deficit has been shown to be an applicable value for determination of the irreversible shock period.¹³ However, the measurement of oxygen deficit is quite hard and invasive monitorization is required. Lactate is a parameter which is being employed for the evaluation of the severity of the shock.¹⁴ Serious hemorrhage and shock are correlated with tissue perfusion and oxygen distribution. As a result, the oxidative metabolism of mitochondria is disrupted and intracellular metabolism shifts to anaerobic glycolysis which results in formation of lactate. Lactic acidosis is mentioned as a beneficial indicator for determination of threshold value of anaerobic metabolism.^{15,16} Previous studies have showed that during hemorrhagic shock lactate level rises whereas it starts to drop in patients subjected to treatment.^{17,18} Kapoor et al.¹⁹ formed a hemorrhagic shock model in dogs and detected a progressive rise in lactate level among dogs subjected to shock. The groups treated with blood exhibited a decrease of lactate level without reaching the level before shock.¹⁹ In the present study, we found a progressive increase during shock in lactate values of the groups subjected to shock, and we detected that it dropped again in the treated groups. While we determined a statistically significant difference between the blood + SF group and sham group, there was no difference between the blood + piracetam and sham group. The improvement in blood + piracetam group was better than that in blood + SF group.

As the hemorrhagic shock advances, the concentration of bicarbonate drops, base deficit rises, and pH decreases. Base deficit value is calculated by blood gas analysis and provides information on tissue acidosis and indirect tissue perfusion. An elevated base deficit shows correlation with presence and severity of shock.^{20,21,22} In a hemorrhagic shock model

induced in dogs, Kapoor et al.¹⁹ detected a decrease in pH and deepening of metabolic acidosis. They observed a rise in blood pH and recovery from acidosis. Moreover, the same investigators showed a drop in bicarbonate values as the shock progressed and found post-reinfusion pH and bicarbonate values reaching the same levels they had before shock in subjects submitted to 2-hour shock. The group treated with 4-hour shock did not show a significant improvement in HCO₃ and pH after the reinfusion.¹⁹ In a 180-minute prolonged hemorrhagia setting, Yao et al.²³ determined a remarkable decrease in blood pH and a rise in metabolic acidosis and base deficit values. Another study performed on pigs revealed a significant rise in base deficit values in two groups which have been subjected to hemorrhagic shock as to have a 40mmHg blood pressure in 30 minutes compared to the group which exhibited 50mmHg blood pressure. They also showed a greater increase of oxygen consumption in that group.²⁴ In consistence with the studies above, we determined a drop in pH values, increase in base deficit values, and formation of metabolic acidosis in the groups subjected to hemorrhagic shock. Following treatment, we observed an improvement in those values, however, we found no difference between the piracetam treatment group and control group.

In conclusion, the inclusion of piracetam in the hemorrhagic shock treatment can benefit in management of blood lactate levels and reduction of liver damage occurring in hemorrhagic shock. However, further studies are needed on use of additional agents for reducing the liver damage persisting throughout the hemorrhagic shock and after the treatment process.

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