# Effect of pentoxifylline and indomethacin on rabbits with endotoxin induced disseminated intravascular coagulation (DIC) and comparison with heparin

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## ABSTRACT

We evaluated the effects of pentoxifylline and indomethacin and heparin in a rabbit model of disseminated intravascular coagulation (DIC) induced by infusion of 100 µg/kg/hour of *Escherichia coli* endotoxin lipoplysaccharide (LPS) for 6 hour. Heparin, indomethacin, pentoxifylline or saline were administered simultaneously with LPS. In addition, a control group was formed which was administered only saline. Hemostatic markers at 0, 1/2, 2, and 6 hour as well as histopathologic changes in the organs and the mortality at 24 hour were determined. The infusion of LPS caused a severe impairment in hemostasis and fibrin accumulation in the pulmonary vasculature. Heparin significantly improved hemostatic impairment and reduced the fibrin accumulation in the pulmonary vasculature. Pentoxifylline and indomethacin had no significant effect on DIC, except that pentoxifylline prevented the decrement in platelet count slightly ($p < 0.05$). None of the drugs, including heparin, had any effect on mortality. As a result, the prevention of the synthesis of only one cytokine or autocoid is not considered enough to control the results of endotoxemia.

**Key Words:** DIC, Endotoxin, Indomethacin, Pentoxifylline, Heparin.

## ÖZET

### Endotoksin ile yaygın damar içi pıhtılaşma oluşturulan tavşanlarda indometazin ve pentoksifilinin etkileri ve heparin ile karşılaştırma

Çalışmamızda pentoksifilin, indometazin ve heparinin 100 µg/kg/saat *Escherichia coli* endotoksin (LPS) infüzyonu ile tavşanlarda oluşturulan yaygın damar içi pıhtılaşma (YDP) modeli üzerindeki etkileri değerlendirildi. LPS ile aynı anda heparin, indometazin, pentoksifilin veya %0.9 NaCl verildi. Ek olarak, %0.9 NaCl'ün tek başına verildiği bir kontrol grubu oluşturuldu. 0., 1/2., 2. ve 6. saatte hemostatik göstergeler, ayrıca organlardaki histopatolojik değişiklikler ve 24. saatteki mortalite tespit edildi. LPS infüzyonu hemostazda ağır bozukluklara ve akciğer damarlarında fibrin birikimine neden oldu. Pentoksifilinin trombosit sayısındaki düşmeyi hafif

düzeyde engellemesi dışında (p< 0.05), pentoksifilin ve indometazinin YDP üzerinde belirgin etkisi görülmedi. Heparin dahil, uygulanan ilaçlardan hiçbiri mortalite üzerinde etkili değildi. Sonuç olarak, tek bir sitokin veya otokoidin sentezinin engellenmesinin endotokseminin sonuçlarını kontrol etmek için yeterli olmadığı düşünüldü.

**Anahtar Kelimeler:** YDP, Endotoksin, İndometazin, Pentoksifilin, Heparin.

## INTRODUCTION

Disseminated intravascular coagulation (DIC), which is the clinical outcome of various diseases, is a syndrome with a very high mortality rate. Bacterial infection, in particular septicemia, is the most common entity associated with DIC[1]. In Gram-negative bacteria-induced sepsis, endotoxin or lipopolysaccharide (LPS), a constituent of the membrane of Gram-negative bacteria, is mostly responsible for the inflammatory effects and procoagulant responses appearing in sepsis and exerts its effects through proinflammatory cytokines[1,2].

Tumor necrosing factor-alpha (TNF-α), a pivotal proinflammatory cytokine, plays an important role in hemostatic impairment and DIC observed in sepsis[1,3-5]. Pentoxifylline, a xanthine derivative that blocks endotoxin-induced transcription of the TNF-α gene, has been found beneficial in the experimental sepsis models[6-10].

On the other hand, in Gram-negative infections - cytokines, which are induced by LPS - trigger the release of prostaglandins and other autocoids from inflammatory cells[11,12]. It was reported that inhibitors of prostaglandin synthesis, including indomethacin, had beneficial effects in sepsis and endotoxemia[12].

In spite of positive effects of prostaglandin synthetase inhibitors and pentoxifylline on sepsis, there are not enough studies in the literature evaluating the effects of these drugs on hemostatic impairment and DIC appearing in sepsis. Therefore, in this study, we evaluated the effects of pentoxifylline-with known anti-TNF-α effect-and indomethacin-which is a strong inhibitor of prostaglandin synthesis-in an experimental DIC model formed with *Escherichia coli* endotoxin and compared their effects with the effects of the classical anticoagulant heparin to determine the efficacy of these drugs in the treatment of DIC.

## MATERIALS and METHODS

### Experimental Model

This experimental study was approved by the ethical committee of Trakya University, Edirne. Forty male New Zealand white rabbits (weight 2.1 to 3.4 kg) were used in the study. All rabbits were kept in the same environmental condition and fed a commercial rabbit diet for at least 10 days before the experiment. Animals were anaesthetized by an intramuscular injection of 30 mg/kg ketamin hydrochloride and 5 mg/kg xylazin followed by intramuscular boosts of ketamine hydrochloride (10 to 30 mg/kg/hour) throughout the experiment. Except in the control group, DIC was induced in all rabbits by the intravenous infusion of 100 μg/kg/hour LPS (*E. coli* serotype 0111:B4-Sigma) for 6 hour in 60 mL (10 mL/hour) saline into the marginal ear vein. Rabbits in the control group (8 rabbits) were administered a total of 120 mL saline for 6 hour into both ear veins.

The rabbits to be included in each group were randomly selected. In addition to the control group, four groups -each including eight rabbits- were formed. LPS group was given saline as placebo (10 mL/hour) for 6 hour; heparin group was given 20 IU/kg/hour heparin for 6 hour in 60 mL saline; indomethacin group was given 10 mg/kg indomethacin in 10 mL saline by bolus injection 15 minutes before LPS infusion

and also saline as placebo (10 mL/hour) for 6 hour; pentoxifylline group was given 30 mg/kg pentoxifylline in 10 mL saline by bolus injection 15 minutes before LPS infusion and also 20 mg/kg/hour pentoxifylline for 6 hour in 60 mL saline.

Surviving rabbits were sacarificed 24 hour after the onset of LPS infusion by ketamine overdose. All rabbits underwent autopsy for histological examination.

**Laboratory Methods**

Blood samples were taken before LPS infusion, and at 5 hour, 2 houre and 6 hour after the onset, a catheter was inserted into the femoral artery.

Blood for platelet counts was collected into tubes containing K3-EDTA. Blood for coagulation tests was collected into tubes containing 3.2% citrate. Platelet-poor plasma was obtained by centrifugation of blood samples with citrate at 1600 g for 20 minutes at 4°C and stored at -80°C until assay.

A Coulter STKS automatic analyzer (Beckman Coulter) was used to count platelets.

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were measured using commercially available kits (Diagnostica Stago, France) on ST4 instrument. Fibrinogen was measured by Clauss method.

**Histological Examination**

Pulmonary, renal and hepatic tissue sections were prepared, fixed in formalin, embedded in paraffin, stained with hematoxylin-eosin and examined for histopathological changes.

**Statistical Analysis**

**Within groups:** Friedman test and Wilcoxon test were used to compare baseline values of the hemostatic parameters with values obtained at 5 hour, 2 and at 6 hour.

**Among groups:** In all groups, the baseline values were subtracted from the values obtained at 5 hour, 2 hour and, 6 hour. The calculated differences were compared among the groups using the Kruskal Wallis test and Mann-Whitney U tests. For comparison of pathological changes (presence of pulmonary fibrin accumulation), the Kruskal Wallis test followed by the Mann-Whitney U test was used.

**RESULTS**

Table 1 shows the changes in hemostatic parameters in the control (saline) and LPS groups. In the control group of rabbits, no changes were observed in the analyzed parameters. In the LPS group, a significant prolongation of PT and aPTT and decrease in plasma fibrinogen level and platelet count were observed.

**Table 1. Hemostatic parameters at baseline and at 5 hour, 2 hour and 6 hour in the control and LPS groups**

| Groups | Time | PT (sec) | aPTT (sec) | Fibrinogen (mg/dL) | Platelets (/µL) |
|---|---|---|---|---|---|
| Control (saline) | Baseline | 7.68 ± 0.13 | 17.11 ± 1.52 | 479.9 ± 41.4 | 522500 ± 60675 |
| | 0.5 hour | 7.77 ± 0.14 | 15.50 ± 1.40 | 477.9 ± 56.4 | 490625 ± 57992 |
| | 2 hour | 7.78 ± 0.19 | 14.13 ± 1.55 | 460.3 ± 57.2 | 481500 ± 58056 |
| | 6 hour | 7.72 ± 0.13 | 16.78 ± 1.54 | 445.2 ± 48.00 | 463000 ± 56898 |
| LPS | Baseline | 7.83 ± 0.33 | 17.38 ± 1.00 | 495.4 ± 26.7 | 650 875 ± 29039 |
| | 0.5 hour | 8.21 ± 0.22 | 15.40 ± 0.56* | 412.9 ± 36.3* | 445 875 ± 29681* |
| | 2 hour | 8.91 ± 0.40 | 18.18 ± 0.76 | 406.9 ± 17.7* | 354 625 ± 25455* |
| | 6 hour | 14.81 ± 1.33* | 33.13 ± 2.67* | 237.2 ± 34.9* | 129 625 ± 36140* |

Data shown as mean ± SEM, * $p < 0.05$ when compared to the basal value, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, LPS: Lipopolysaccharide.

Table 2 shows the changes in hemostatic parameters in the treatment groups. Heparin significantly improved the hemostatic abnormalities observed in the LPS group (Figures 1-4); no significant prolongation of aPTT and no decrease in fibrinogen level were observed in the heparin group. There was a prolongation of PT and a decrement in platelet count in the heparin group but when compared with the LPS group, heparin treatment significantly prevented the prolongation of PT ($p< 0.001$) (Figure 1) and decrement in platelet count ($p< 0.05$) (Figure 4) observed at the $6^{th}$ hour.

Indomethacin treatment did not significantly prevent the prolongation of PT and aPTT (Figure 1,2), northe decrement in plasma fibrinogen level and platelet count observed in the LPS group (Figure 3,4). Similarly, pentoxifylline treatment did not significantly prevent the prolongation PT and aPTT northe decrement in plasma fibrinogen level (Figures 1-3); however, it prevented a further decrement in the platelet count observed in the LPS group ($p< 0.05$) (Figure 4).

None of the rabbits in the control group and ally of the rabbits in the LPS group had fibrin accumulation in their pulmonary vasculature. There was fibrin accumulation in the pulmonary vasculature of two rabbits, that were administered heparin (2/8 rabbits), and this was significant ($p< 0.05$) when compared with the LPS group (Figure 5). Seven rabbits in the indomethacin group and three rabbits in the pentoxifylline group had fibrin accumulation in the pulmonary vasculature. In spite of the decrement in fibrin accumulation in these groups, especially in the pentoxifylline group, no significant difference was found when compared with the LPS group. Excluding the control group, the DIC-induced histopathological changes in the kidneys and in the liver were not significantly different among the groups.

All rabbits in the control group survived. In both the LPS and heparin group, two of eight rabbits survived; and in both the indomethacin and pentoxifylline group one of eight rabbits was alive after 24 hours of the onset of the experiment. There were no significant differences among groups, excluding the control group.

**Table 2. Hemostatic parameters at baseline and at 0.5 hour, 2 hour and 6 hour in the treatment groups**

| Groups | Time | PT (sec) | aPTT (sec) | Fibrinogen (mg/dL) | Platelets (/µL) |
|---|---|---|---|---|---|
| LPS | Baseline | 7.55 ± 0.17 | 18.35 ± 1.9 | 521.4 ± 41.7 | 475875 ± 79364 |
| + | 0.5 hour | 7.50 ± 0.22 | 18.80 ± 1.98 | 518.9 ± 53.6 | 284375 ± 68392* |
| Heparin | 2 hour | 7.77 ± 0.24 | 22.55 ± 3.36 | 549.5 ± 56.9 | 255250 ± 54799* |
| | 6 hour | 10.12 ± 0.54* | 21.36 ± 2.13 | 436.3 ± 73.2 | 139750 ± 37480* |
| LPS | Baseline | 7.76 ± 0.17 | 18.0 ± 1.60 | 561.1 ± 52.8 | 605125 ± 67483 |
| + | 0.5 hour | 7.75 ± 0.15 | 15.21 ± 1.31* | 492.3 ± 45.5 | 374375 ± 43992* |
| Indomethacin | 2 hour | 8.12 ± 0.20 | 17.51 ± 1.58 | 521.8 ± 69.8 | 355125 ± 60206* |
| | 6 hour | 12.21 ± 0.52* | 28.47 ± 2.07* | 358.8 ± 40.8* | 78000 ± 17210* |
| LPS | Baseline | 7.76 ± 0.22 | 18.60 ± 1.59 | 459.2 ± 76.1 | 482750 ± 25359 |
| + | 0.5 hour | 8.10 ± 0.26 | 15.73 ± 1.65* | 427.5 ± 79.6 | 353875 ± 31164* |
| Pentoxifylline | 2 hour | 9.55 ± 0.46* | 21.11 ± 2.22 | 345.2 ± 73.0* | 271625 ± 36878* |
| | 6 hour | 13.47 ± 0.71* | 28.60 ± 2.84* | 176.9 ± 24.3* | 136000 ± 39293* |

Data shown as mean ± SEM, * $p< 0.05$ when compared to the basal value, LPS: Lipopolysaccharide, PT: Prothrombin time, aPTT: Activated partial thromboplastin time.

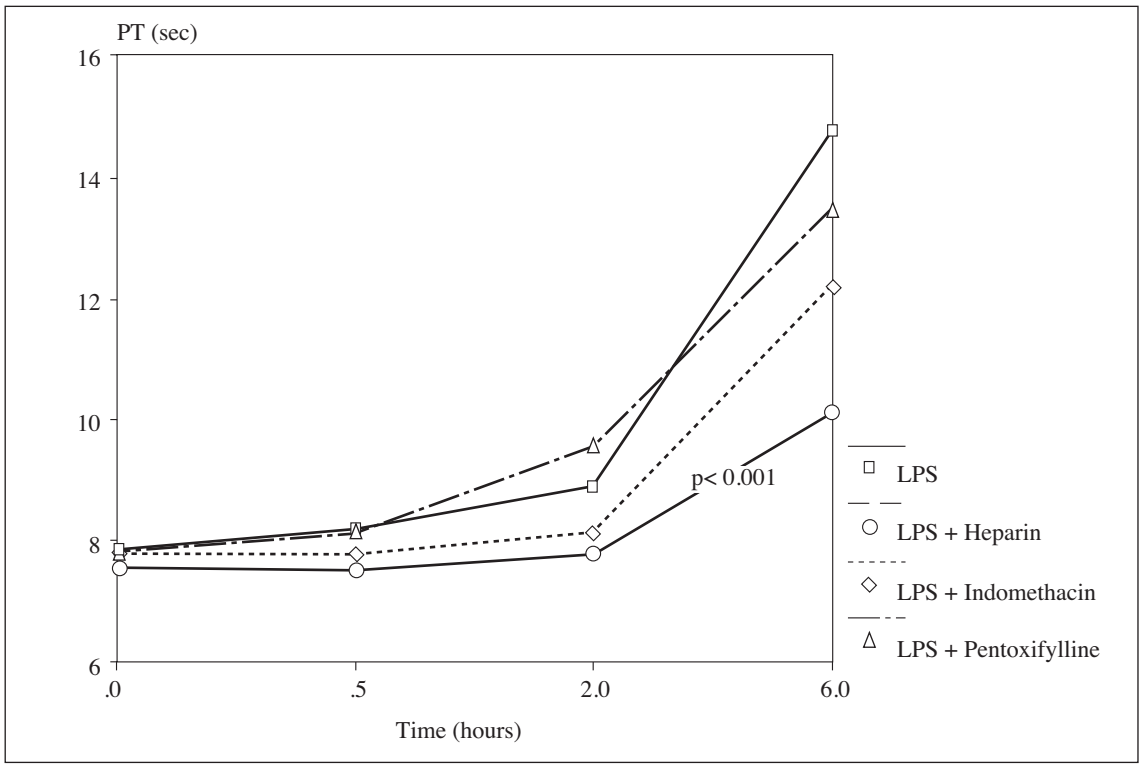


**Figure 1.** The change in PT over time in the LPS and treatment groups. The p value indicates the difference from the LPS group.

## DISCUSSION

In this study, we evaluated the effects of pentoxifylline and indomethacin on an experimental DIC model formed with *E. coli* endotoxin and compared their effects with the effects of heparin in order to determine the value of antiinflammatory and anticytokine therapies in the treatment of DIC.

Similar to the results of previous studies[13,14], the infusion of endotoxin caused severe DIC in our study characterized by the prolongation of PT, and aPTT and decrement in plasma fibrinogen level and platelet count. Heparin significantly limited the consumption coagulopathy induced by endotoxin, and decreased fibrin accumulation in the pulmonary vasculature. However, pentoxifylline and indomethacin had no significant effect on DIC. Pentoxifylline prevented the decrement in platelet count slightly. None of the drugs, including heparin, had any effect on mortality rate.

It has been proposed that TNF-α - together with other cytokines - has an important role in triggering DIC, especially in sepsis[3,5]. Many studies have shown the role of TNF-α in coagulation activation appearing in sepsis[4,15-17], however, some other studies, which used monoclonal antibodies directed against TNF-α suggested that TNF-α was not the main mediator of endotoxin-induced activation of coagulation[18]. The depression of anticoagulant mechanisms such as protein C activation and impaired fibrinolysis due to an increase in plasminogen activator inhibitor (PAI)-1 have been found to be related to TNF-α in sepsis[1,19,20]. A recent study stated that TNF-α led to platelet-aggregating factor (PAF) production by stimulating granulocytes and that PAF induced TNF expression in a platelet-dependent manner[3].

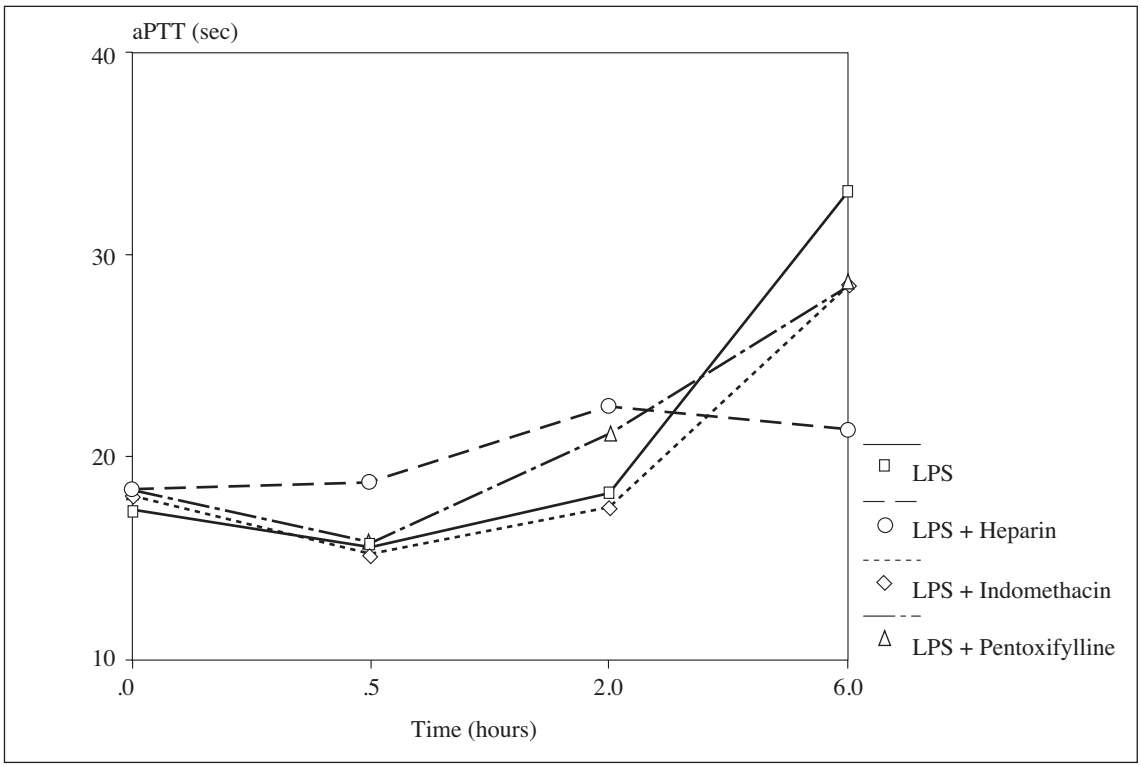


**Figure 2.** The change in aPTT over time in the LPS and treatment groups. The p value indicates the difference from the LPS group.

Pentoxifylline, a derivative of methylxanthine, prevents the gene transcription of TNF-α, there by inhibiting its production[21,22]. It was reported that pentoxifylline decreased the serum TNF-α level and increased platelet count in cancer patients with DIC[23]. Based on these observations, pentoxifylline has been frequently used in sepsis, burns and animal models in which sepsis has been induced. Most of these studies demonstrated that pentoxifylline had beneficial effects in these conditions and decreased mortality[6-10]. In the literature, pentoxifylline usually showed its beneficial effects in experimental models when it was used at a low dose for a long period of time[6]. The explanation for pentoxifylline not increasing survival in our study might be that our DIC model was severe and pentoxifylline was used at high doses for a short period of time. In literature data, it is not clear why low-dose - and not high-dose - pentoxifylline increases survival in sepsis. It has been suggested that a high concentration of pentoxifylline inhibits the production of superoxide and phagocytosis in vitro; however, at low doses it clearly increases chemotaxis and phagocytosis[24]. In addition, it was reported that high-dose pentoxifylline inhibits the production of interleukin (IL)-1 -important in host defenses- completely[25].

There are not enough studies in the literature examining the effects of pentoxifylline on hemostatic parameters. It was reported that the administration of pentoxifylline increased the platelet count in cancer patients[23]. In line with this observation, we found that pentoxifylline administration prevented the decrement in platelet count slightly and that was statistically significant.

Studies in both human subjects and experimental animals have implicated the eico-

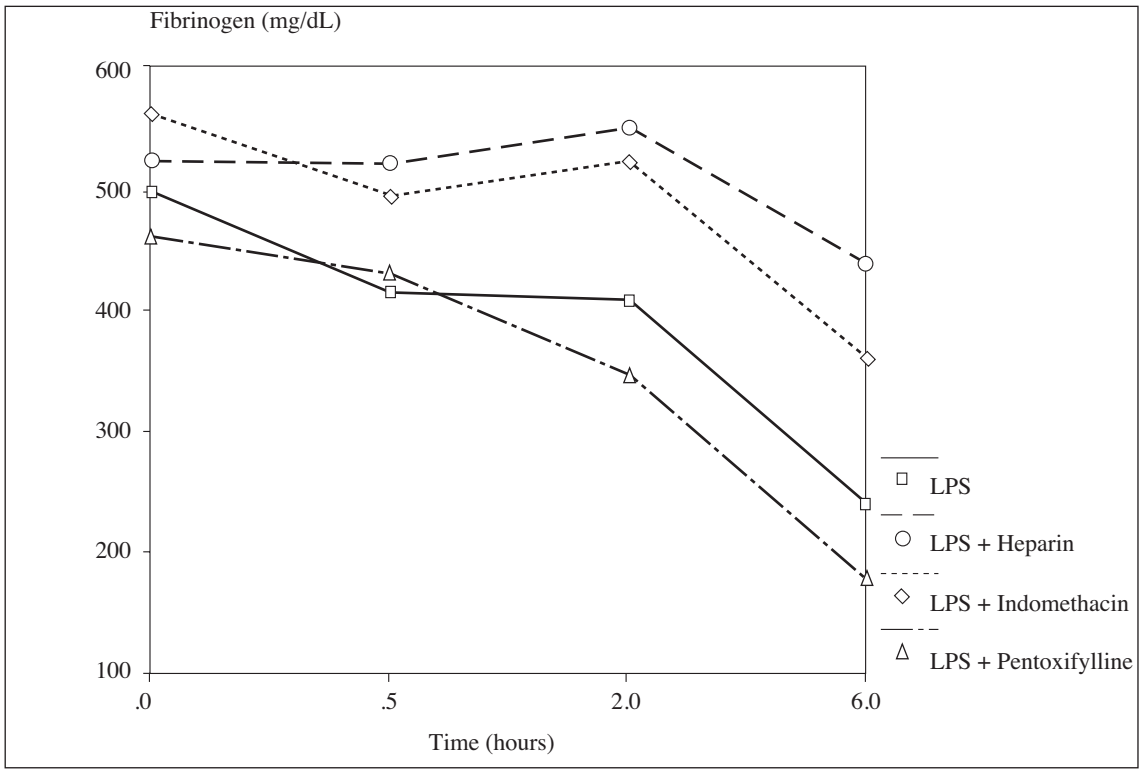


**Figure 3.** The change in fibrinogen plasma level over time in the LPS and treatment groups. The P value indicates the difference from the LPS group.

sanoids (particularly thromboxane A2, leukotriene B4 and cysteinyl-leukotrienes), PAF and bradykinin in the pathogenesis of endotoxemic shock, septic shock, multiple organ system failure and adult respiratory distress syndrome (ARDS)[12]. In Gram-negative infections, cytokines appear with the induction of LPS and they trigger the release of prostaglandins and other autocoids from inflammatory cells[11,12]. It was stated that these cytokines increased eicosanoid production with the activation of phospholipase A2, upregulation of cyclooxygenase (COX)-2 expression and the posttranslational stabilization of the mRNA of COX-2[26-28]. It was demonstrated that the incubation of LPS with monocytes/macrophages in vitro led to the induction of COX-2 and the production of prostaglandins[29].

Various inhibitors of prostaglandins synthesis have been used in the treatment of sepsis and endotoxemia. With very few exceptions, the pharmacological inhibition of cyclooxygenase has been shown to improve systemic hemodynamics, preserve pulmonary function, limit oxidant-mediated tissue damage and prevent death in animals challenged with endotoxin or viable bacteria or in animals with experimentally induced peritonitis[30-37]. In our model, we evaluated the effects of indomethacin mainly on hemostatic parameters. There are not enough studies in the literature evaluating the effects of cyclooxygenase inhibition on hemostatic impairment and DIC in sepsis. In our study, indomethacin did not have any significant effect on hemostatic parameters impaired in endotoxemianor not did it have any effect on mortality in this study. Studies evaluating mortality are different in some aspects from our study. Usually, sepsis in these models was less severe than in our study and the durati-

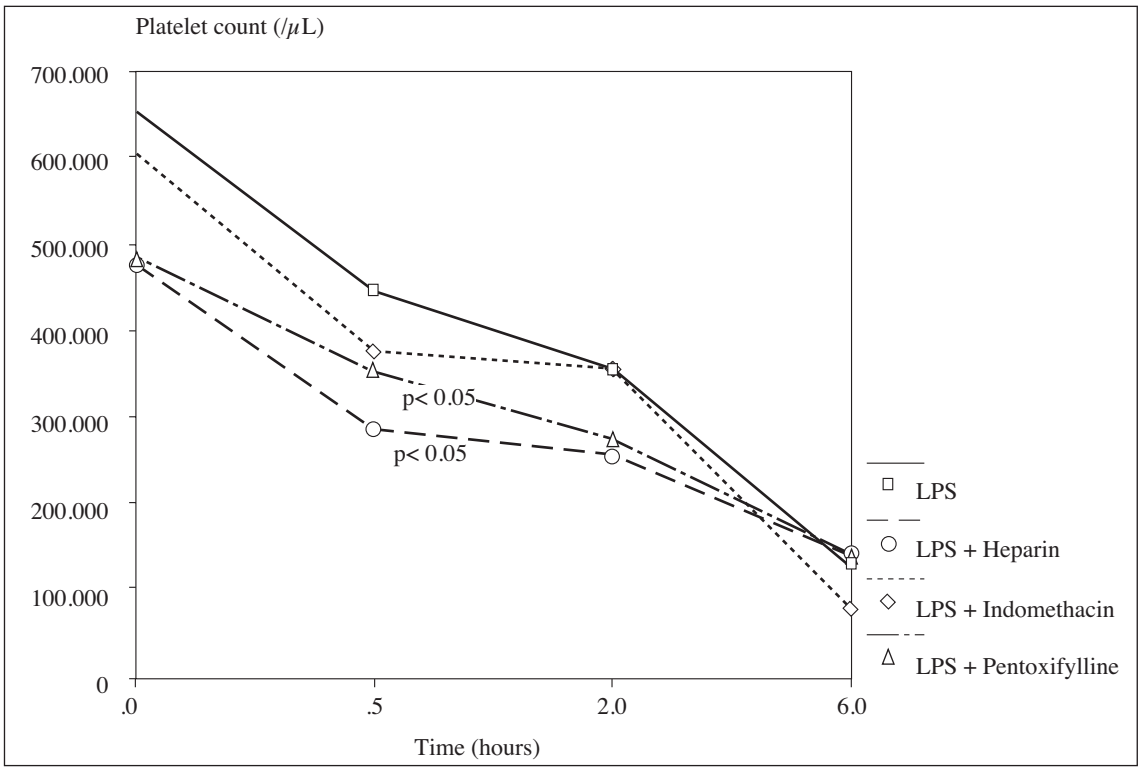


**Figure 4.** The change in platelet count over time in the LPS and treatment groups. The p value indicates the difference from the LPS group.

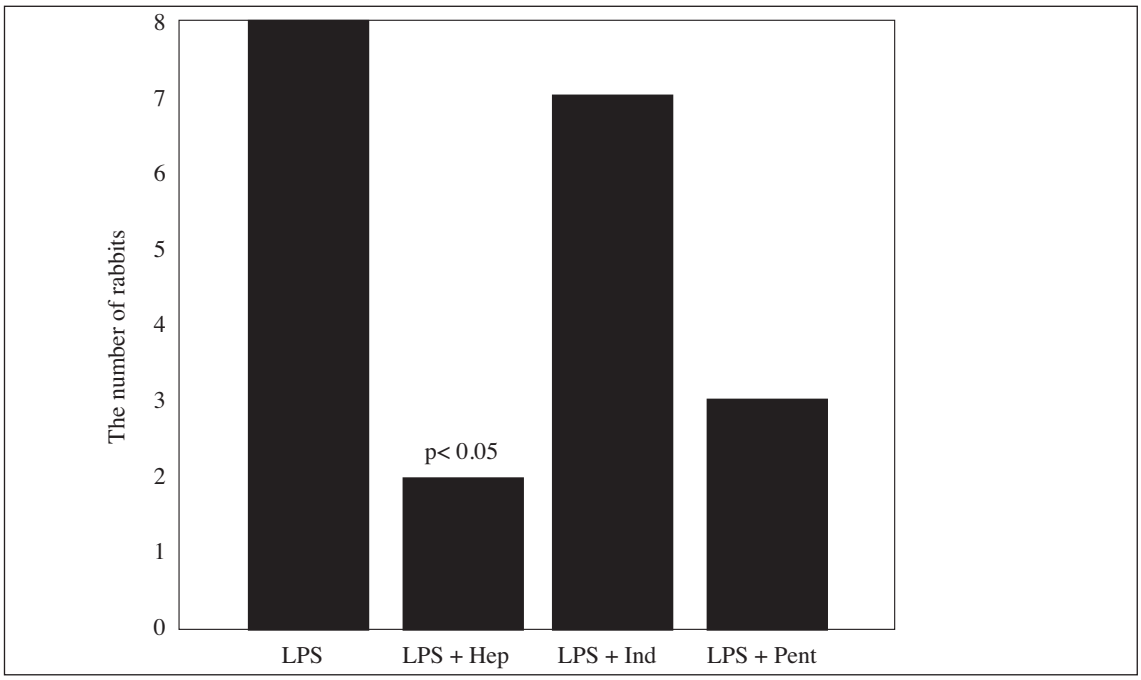


**Figure 5.** The number of rabbits with fibrin accumulation in the pulmonary vasculature in the LPS and treatment groups. The p value indicates the difference from the LPS group.

on of sepsis was longer than our endotoxemia model and used various drugs in different dosages for cyclooxygenase inhibition. In addition, our study groups were small and this may result in inadequacy when evaluating mortality.

Consequently, pentoxifylline and indomethacin did not show any significant impacts on coagulation tests, fibrin accumulation and mortality. Heparin suppressed consumption coagulopathy significantly; nevertheless, it did not improve mortality. When it is considered that many cytokines, autocoids, chemokines and oxidation products take a role in the pathogenesis of endotoxemia, septic shock and secondary DIC the prevention of the synthesis of only one cytokine or autocoid does not seem sufficient to control the results of endotoxemia.

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