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Original Study

Comparison of Antithrombin III and Pentoxifylline Treatments in Gram Negative Sepsis Patients Developing Disseminated Intravascular Coagulation

Dissemine İntravasküler Koagulasyon Gelişen Gram Negatif Sepsis Hastalarında Antitrombin III ve Pentoksifilin Tedavilerinin Karşılaştırılması

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Ethics Committee Approval: This study approved by the Istanbul University Cerahpasa Medical Faculty Ethic Committee, 14 March 2003, 2003/1071.
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ABSTRACT

Objective: *The aim of this study was to evaluate the effects of antithrombin III (AT III) and pentoxifylline treatments on the gram negative septic patients with disseminated intravascular coagulation (DIC).*
Method: *For six days after plasma AT III activity dropped lower than 80% in Gram-patients who developed DIC were treated with AT III (90-120 IU/kg/day in 6 hours) or pentoxifylline (1.5 mg/kg/h in 6 hours) Fibrinogen, FDP, D-dimer, complete blood count, AT III activity, and DIC scores were calculated and recorded.*
Results: *The coagulation tests, AT III activity and FDP started to improve from the second day of treatment with both treatments ($p<0.05$). D-Dimer started to decrease on the second day of treatment with pentoxifylline ($p<0.001$) and fourth day of AT III treatment ($p<0.05$). Fibrinogen levels decreased on the second day of pentoxifylline treatment ($p<0.05$) and on the last day of AT III treatment ($p<0.001$). DIC scores started to decrease on the last day of treatment with AT III treatment ($p<0.001$) and on the third day of treatment with pentoxifylline ($p<0.05$).*
Conclusion: *Both ATIII and pentoxifylline treatments had positive effects on fibrinogen, FDP, D-Dimer, AT III activity and DIC scores in patients with Gram-negative sepsis who developed DIC.*

Keywords: *Gram negative sepsis, disseminated intravascular coagulation, antithrombin, pentoxifylline*

ÖZ

Amaç: *Çalışmamızda Disemine İntravasküler Koagülasyon (DİK) gelişen Gram negatif sepsis hastalarında Antitrombin III (AT III) ve Pentoksifilin tedavilerinin etkinliğini karşılaştırmayı amaçladık.*
Yöntem: *DiK gelişen gram negatif sepsis hastalarında AT III aktivitesinin %80'in altına düştüğü günü takipeden 6 gün hastaların bir kısmına 90-20 IU/kg/gün 6 saat olacak şekilde AT III, diğer kısmına 1,5 mg/kg/saat 6 saat olucak şekilde pentoksifilin tedavisi uygulandı. Fibrinojen, FDP, D-Dimer, tam kansayımı, ATIII aktivitesive DİK skorlarına bakıldı.*
Bulgular: *Koagülasyon testleri, AT III aktivitesi ve FDP her iki tedavi ile tedavinin 2. gününden itibaren iyileşmeye başladı ($p<0,05$). D-Dimer Pentoksifilin tedavisiyle tedavinin 2. gününden ($p<0,001$), AT III tedavisiyle 4. gününden itibaren ($p<0,05$) düşmeye başladı. Fibrinojen düzeyleri Pentoksifilin tedavisinin 2. günü ($p<0,05$), AT III tedavisinin son gününde ($p<0,001$) düştü. DiK skorları Pentoksifilin tedavisiyle tedavinin 3. gününde ($p<0,05$) AT III tedavisiyle tedavinin son gününde ($p<0,001$) düştü.*
Sonuç: *olarak DİK gelişen gram negatif sepsis hastalarında AT III ve Pentoksifilin tedavilerinin her ikisininde koagülasyon testleri, Fibrinojen, FDP, D-Dimer, AT III aktivitesive ve DİK skorları üzerine olumlu etkisi vardır.*

Anahtar kelimeler: *Gram negatif sepsis, dissemine intravasküler koagulasyon, antitrombin, pentoksifilin*

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INTRODUCTION

Sepsis is a systemic response to infection in a clinical syndrome pattern. Disseminated Intravascular Coagulation (DIC) is a coagulopathy that develops in about 35% of severe sepsis cases[1].

Pathophysiology of DIC involves activated coagulation system which results in consuming multiple clotting factors. In Systemic Inflammatory Response Syndrome (SIRS) in sepsis proinflammatory cytokines that promote coagulation by perturbed endothelial cells and activated mononuclear cells are generated. Coagulation is initiated by proteins expressed on these endothelial and mononuclear cells. Monocyte chemo-attractant protein-1 and interleukin (IL)-6 in monocytes, fibroblasts, and mesothelial cells are stimulated by thrombin[2]. During DIC induced by sepsis- activated coagulation, impairment of anticoagulant mechanisms including antithrombin (AT) system and interrupted fibrin removal because of depressed fibrinolytic system play roles in microthrombus formation. This thrombus formation contributes to oxygen delivery impairment and organ dysfunction[3,4].

AT is a 58 kDa molecule with a single-chain glycoprotein. It has multiple biologically important properties as a plasma-derived serine protease in hemostasis. It has anticoagulant and anti-inflammatory properties in the coagulation cascade. Factor X and thrombin lead to release of pro-inflammatory mediators in inflammation process. Anti-inflammatory properties and anticoagulant activities of AT have different mechanisms. By binding to the glycosaminoglycans, and suppressing capillary leakage, AT is involved in the protection of endothelial cells and exerts an anti-inflammatory effect in sepsis[4-6]. Excessive thrombin generation increases vascular permeability degrades acceleration of AT and impairs synthesis of AT in the liver with resultant decrease in AT activity in DIC. Decreased AT activity is associated with severity of sepsis and high mortality and AT supplementation is recommended in patients with sepsis, and lower AT activity[7,8].

Pentoxifylline (PTX), a nonspecific phosphodiesterase inhibitor, is a 3,7-dimethyl-1-(5-oxohexyl)-xanthine in chemical structure. In experimental animals with sepsis, treatment with PTX also lowers circulating levels of TNF-alpha[9]. PTX can induce the release of cell-derived endogenous regulators and decrease the extent of inflammatory reactions. For instance, PTX acts on intracellular cyclic AMP- like adenosine, prostacyclin, and prostaglandins of the E series and potentiates the anti-inflammatory actions of them. As a result, studies have demonstrated that PTX can inhibit cytokine production, platelet aggregation and oxygen-radical production in sepsis and DIC[10]. Consequently, PTX improves tissue oxygenation by increasing the microcirculatory perfusion[11,12].

In the literature very small number of studies have evaluated the efficacy of AT III and PTX treatments. The aim of this study was to evaluate the effects of AT III and PTX on DIC scores. H0 hypothesis is expressed as follows “In adult patients with Gram-negative sepsis with DIC, activities of AT III and PTX treatments differ from each other.’’

MATERIAL and METHOD

The study protocol was approved by the Ethics Committee of Istanbul University Cerrahpasa Medical Faculty (14 March, 2003, 2003/1071). Informed consent was taken from the relatives of the patients enrolled in this study.

This prospective study was conducted with 30 Gram-negative sepsis-induced DIC patients in Emergency Reanimation Department of Istanbul University Cerrahpasa Medical Faculty in 2002. Patients with active bleeding and known allergy for AT III (Kybernin P, Farma-Tek, Germany) and/or pentoxifylline (Trental amp, Aventis, Germany) were excluded, and the duration of the study was 7 days.

The first 24 hour-APACHE II scores were calculated and recorded. Patients who had gram negative

bacteria in endotracheal aspirate, urine culture and their SOFA score ≥2 have been diagnosed with sepsis. The Gram-negative septic patients who developed DIC were included in the study. When plasma AT III activity was lower than 80%, then patients were randomly divided into two groups using a computer-generated randomization scheme. AT group (n=10) received AT III 90-120 IU/kg/day in 6 hours for 6 days. The PTX group (n=20) received 1.5 mg/kg/h of PTX in 6 hours in 6 days. Enoxaparin (Clexane 0.4 ml, Aventis) was administered subcutaneously to all patients daily. Fibrinogen, FDP, D-dimer, complete blood count, glucose, AT III, coagulation tests were performed and recorded from the blood samples taken in the morning of each study day. Daily heart rate, mean invasive arterial blood pressure, central venous pressure, and axillary body temperature were measured with Datex Ohmeda S5 (USA) and recorded in all study days. Arterial blood gas values were also measured and recorded. DIC scores[13] were daily calculated and recorded during the study.

The data were expressed as mean and standard deviation (SD) in tables. The demographic data of the groups were compared with the T-Test. Differences in-groups were statistically analyzed by repeated measurement variant analysis (ANOVA) and the T-Test was used between the groups. The groups were compared to verify the differences at a significance level set at $p<0.05$ using SPSS 14 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Demographic data of two groups were not statistically different ($p>0.05$) (Table 1). There was no statistical difference in hemodynamic parameters between the two groups ($p>0.05$). There were also no differences between groups in hemoglobine, blood glucose, platelet counts and mean body temperature measurements ($p>0.05$).

Lactate values were statistically significantly decreased in both groups during treatment ($p<0.001$). Coagulation tests (PT, PT activity, INR and aPTT) showed gradual improvements after the second day of the treatment in both groups and were found to be statistically significant ($p<0.05$) (Table 2).

AT III measurements of the patients increased statistically significantly after the second day of

Table 1. Demographic data of the cases.

	AT III Group	PTX Group
Age (year)	50.26±24.79	55.89±19.94
Weight (kg)	65.84±17.42	73.22±7.27
Gender (F/M)	5/5	5/15
APACHE II	18.16±5.20	16.22±7.37

AT: Antithrombin. PTX: Pentoxifylline

Table 2. Coagulation parameters.

	ATIII				PTX			
	PT	PT Act	inr	aPTT	PT	PT Act	inr	aPTT
1st day	24.6±10.6	48.2±14	2.4±1	69.7±30.7	33.7±23.3	42.5±16	2.6±1	72.7±25.3
2nd day	22±9.9	49.6±20.4	2.5±1.4	62.9±24.7	25.5±8.8	47.3±12	2.4±1.5	63.6±18
3rd day	21.6±11.2	60±20.5	1.9±0.7	59.4±23.4	22.2±6.6^{x}	55±11^{xxx*}	2±0.5^{xxx}	51.6±12^{xxx}
4th day	17.3±10.9^{xxx}	75.3±18.5^{xxx}	1.4±0.4^{xx}	41±6.8^{x}	20±5.4^{xxx*}	63.9±11.2^{xxx}	1.7±0.5^{xxx}	49.7±13^{xxx*}
5th day	16.9±6.9^{xxx}	74±14.8^{xxx}	1.3±0.3^{xx}	40.8±11.8^{x}	18.1±1.5^{xxx}	73.8±10.5^{xxx}	1.5±0.4^{xxx}	44±12^{xxx}
6nd day	14.4±1^{xx}	80±6.6^{xxx}	1.1±0.2^{xx}	41.5±13.4^{x}	17.3±3^{xxx}	80.7±9.4^{xxx}	1.4±0.2^{xxx}	35.5±10.6^{xxx}
7th day	14.1±1.5^{xx}	83±9^{xxx}	1.1±0.2^{xx}	38.4±12^{x}	15.4±3.2^{xxx}	88.7±10^{xxx}	1.2±0.2^{xxx}	32.4±11^{xxx}

^{x}:p<0.05 when in-group 1st day values are encountered.
^{xx}:p<0.01 when in-group 1st day values are encountered.
^{xxx}:p<0.001 when in-group 1st day values are encountered.
*:p<0.05 compared to groups.
AT: Antithrombin. PTX: Pentoxifylline. PT. Platelet time. PT Act: Activated Platelet Time. Inr: International normalized ratio. aPTT: Activated prothrombin time.

Table 3. Antithrombin, Fibrinogen, FDP, D-Dimer Values.

	ATIII				PTX			
	AT	**Fibrinogen**	**FDP**	**D-Dimer**	**AT**	**Fibrinogen**	**FDP**	**D-Dimer**
1st day	51.1±13.6	378.5±146.4	24.4±5	368.7±105.2	54.6±14.2	346.2±144	23±6.4	724.4±364.4
2nd day	60.8±20.7	401±167.6	22.8±4.6	332.4±75.2	61±15.1	259±108.9**	22.2±6.1	698±217
3rd day	71.8±19xxx	427±198	20.8±4.6xx	315.2±77.6	66.3±15.3xxx	272±103*	19.8±6xxx	541±269xxx*
4th day	76.2±17.7xxx	376±123	19±5xxx	267.2±122.7	71.2±13.4xxx	304.6±77.5x*	18.2±6.6xxx	423±218xxx*
5th day	74.2±26.8x	368.7±80.5	16.2±5.6xxx	237.2±139.1x	79.5±11xxx*	337.6±84xx*	15.1±7.4xxx	387±246xxx*
6nd day	86.9±15.7xxx	373.4±71.5	13.8±4.5xxx	224.3±156.4x	81.7±11.9xxx	339.8±81.7x*	13.6±7.9xxx**	342.3±237.7xxx
7th day	94±12xxx	380±97xxx	11.3±5.9xxx	182±139xxx	94.6±13xxx	384±83.3xxx	13±8.1xxx*	307±278xxx*

x:p<0.05 comparison of in-group 1st day values.
xx:p<0,01 in-group 1st day values comparison.
xxx:p<0.001 in-group 1st day values comparison.
**:p<0.05 between groups comparison*
***:p<0.01between groups comparison*
AT: Antithrombin. PTX: Pentoxifylline. FDP: Fibrin degredation products.

the treatments in two groups (p<0.05) and the increase in PTX group was statistically significant than AT group on the 4th day of the treatment. Fibrinogen levels started to decrease statistically significantly in the PTX group on the 3rd day of treatment (p<0.05), but the values were statistically significant at the last day of treatment in the AT III group (p<0.001). The level of decrease in PTX group was statistically significant than the AT group (p<0.05). Statistically significant decrease in FDP began on the 2nd day of the treatments in two groups (p<0.01). D-Dimer started to decrease from the 2nd day of the treatment in the PTX group (p<0.001) and 4th day of the treatment in the AT III group (p<0.05) (Table 3).

The DIC scores of the patients started to decrease on the 3rd day of the treatment in the PTX group (p<0.05), while they were statistically significant in the AT III group on the 6th day of treatment (p<0.001). The difference between the groups is statically significant at the last day of treatments (p<0.05) (Table 4).

Table 4. DIC score values.

	1st day	2nd day	3rd day	4rd day	5th day	6th day	7th day
AT III	7.6±1.5	7.6±1.3	7.3±1.1	7.1±0.8	7.3±1.4	7.3±1.5	7.2±1.6xxx
PTX	8.2±1.2	8.1±1	7.7±0.8x	7.2±1xxx	7±1xxx	6.5±1xxx	6.3±1xxx*

x:p<0.05 comparison of in-group 1st day values.
xxx:p<0.001 in-group 1st day values comparison.
**:p<0.05 between groups comparison*
AT: Antithrombin. PTX: Pentoxifylline.

On the third day of PTX treatment, if the AT III activity was still low, it was planned to terminate the treatment and switch to AT III treatment. But we did not have such a patient in our study. If active bleeding was observed in our study patients, it was planned to evaluate and reorganize the treatment. However, no active bleeding was observed in our study patients.

DISCUSSION

The appropriate management of DIC itself is a main part of treatment strategies for severe sepsis, because DIC is an independent predictor of mortality in critically ill patients[14]. Increased consumption of activated AT, decreased production by liver, degradation by neutrophil elastase and transportation to the extravascular space are the causes of observing decreased levels of AT in septic patients. Decreased level of AT III activation leads thrombin inactivation and prolongs state of coagulation[4,15].

Decrease in the level of AT activity down to 60% is seen with severe sepsis. While 40% activity of AT III is seen in full blown DIC. Choi et al.[16] reported a correlation between AT and the DIC scores in septic patients. This suggests that AT level is a good indicator of DIC severity.

Retrograde clinical trials studied with patients having sepsis- induced DIC, have shown improve-

ment in patients' outcomes with anticoagulant therapies[8,14,17,18]. Umemura et al.[19] collected and investigated separate meta-analyses of randomized controlled trials for anticoagulant therapy in three different groups of patients with sepsis including patients with sepsis, patients with sepsis-induced coagulopathy, and patients with sepsis-induced DIC. In 24 trials enrolling 14.767 patients, the overall mortality of sepsis patients and the patients with sepsis-induced coagulopathy was not changed with anticoagulant therapy. However, there is significant reductions in mortality rates of the patients with sepsis-induced DIC. Bleeding complication of three groups increased similarly with anticoagulant therapy[20]. Also we used low-molecular weight heparin, and there was no bleeding complications in our patients.

AT III treatment with daily infusion doses of 90-120 mg/kg had been used by Fourrier et al.[21] in septic shock patients with DIC. In our study, the same infusion rate, and doses of AT III were used and we observed improvement in fibrinogen, D-Dimer, platelet counts and coagulation parameters. As a result, we found a decrease in DIC scores in AT III groups. AT III values of our patients have increased gradually since the 2nd day of AT III treatment. We gave higher amount of drug than used in recent studies. Okamoto et al.[4] 22 gave AT (30 IU/kg/day) for 3 days and obtained significantly lower DIC scores and higher recovery rates in these patients than in the control group. Iba et al.[23] studied 60 sepsis- induced DIC patients with 50-80% AT levels. They found that AT at a dose of 30 IU/kg per day given for three days was effective in the modulation of the DIC score and better recovery from DIC in septic patients. They also studied other surveys. They introduced AT III with two different doses of 1500 IU/day and 3000 IU/day given for three days, and subsequently the AT activity dropped below 70% in 729 sepsis-induced DIC patients. Survival rates of low dose group were lower than high dose group. In this study severe bleeding risk was less than 2%, and administration of heparin did not increase the risk[24]. Same investigators substitute same doses in patients having AT III activity below 40%. They found better survival in patients receiving high dose AT III. There were no significant differences in bleeding tendencies between groups[4,25]. We have observed a decrease in DIC scores in patient treated with daily infusion doses of 90-120 mg/kg AT III without any bleeding complications.

Although PTX treatment is recommended in cases with neonatal sepsis[25,27], studies have been also conducted on adult patients[28,29]. Drug doses in the studies with adults were not as high as neonatal patients. Zeni et al.[28] studied patients with septic shock and patients were randomly assigned to receive either PTX (1 mg/kg) followed by an infusion of 1.5 mg/kg/hr for 24 hrs, or placebo. In PTX-treated patients, serum concentrations of TNF at 24 hours were significantly lower compared with controls. Serum concentrations of IL-6 and IL-8 were not different in two treatment groups. There were also no significant differences in any hemodynamic and oxygenation measurements between the two treatment groups[28]. In the study of Boldth et al.[29], PTX was continuously infused over 5 days at a dose of 1.5 mg/kg/hr iv in trauma-PTX group (n=15), sepsis-PTX group (n=15) or saline solution as placebo (trauma-control [n=15], and sepsis-control groups (n=15). Continuous intravenous administration of PTX for 5 days affected the thrombomodulin/protein C/protein S system beneficially in both the trauma and the sepsis patients.

In our study we administered PTX in1.5 mg/kg/h dose that had been used in Boldth's study. Improvement of coagulation parameters was seen after the first day of the PTX treatment. Fibrinogen level, FDP and platelet counts were also improved and as a result DIC scores of these parameters were also decreased. Since the second day of the PTX treatment, AT III levels of the patients have gradually increased.

CONCLUSION

In our study on Gram-negative patients who developed DIC both ATIII and PTX had similar positive ef-

fects on coagulation parameters, fibrinogen, FDP, D-Dimer levels and platelet counts. In both treatments, AT levels started to rise in the early period of treatment and reached normal values at the end of the study. However there is a need for long-term, cost-effective, and larger-scale studies on this issue.

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