

# The efficacy of antithrombin administration in the acute phase of burn injury

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## Summary

Severe burn injury is characterized by the activation of coagulation, decreased fibrinolytic activity and decreased natural anti-coagulant activity. The aim of our study was to investigate the effect of antithrombin (AT) administration on coagulation status and on organ function in the early post-burn period. Thirty-one patients were admitted to the burn intensive care unit and were then randomised into two groups (AT-treated and non-AT-treated) for four consecutive days after thermal injury. The clinical data, coagulation and fibrinolysis parameters were compared and the adverse effects were monitored. Significant differences in the time course of coagulation markers (thrombin/AT complexes, tissue plasminogen activator, D-dimer) were observed between AT-treated and non-AT treated groups. According to

the International Society on Thrombosis and Haemostasis criteria, disseminated intravascular coagulation (DIC) diagnosis was made in 28 of 31 patients. The presence of overt DIC was associated with mortality ( $p < 0.001$ ). The Sequential Organ Failure Assessment (SOFA) score time trend differed significantly between the two investigation groups (decreased in the treated group and did not change in the non-AT-treated group). AT-treated patients had an absolute reduction in a 28-day mortality of 25% as compared to the non-AT-treated group ( $p = 0.004$ ). No treatment related side effects were observed. Treatment with AT seems to affect the coagulation status and reduce multiple organ failure incidence and mortality in the early post-burn period.

## Keywords

Antithrombin, burn injury, coagulation markers, disseminated intravascular coagulation, sequential organ failure assessment score

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## Introduction

A severe burn injury is characterized by an increased production of inflammation and coagulation mediators. The haemostatic imbalance includes the activation of procoagulant pathways, the decreased fibrinolysis, and the impairment of natural anticoagulants activity (1–3).

Early post-burn coagulation and fibrinolysis abnormalities are clinically evident as disseminated intravascular coagulation (DIC) syndrome and may become an important factor in the pathogenesis of organ failure after thermal injury (4–6). DIC has been reported in 30% of post-mortem studies of severely burned patients (7).

Several studies, published recently, suggested that treatment with antithrombin (AT) might be beneficial to patients with burn-related DIC as it may ameliorate organ dysfunction and

possibly reduce mortality (8–10). AT is a broad-spectrum plasma serine protease inhibitor with marked anticoagulant and anti-inflammatory action (11–14). It should be noted that the anti-inflammatory properties of AT are only seen in the absence of heparin (15, 16). AT levels are rapidly depleted as a result of complex formation with thrombin, increased loss in interstitium due to impaired vascular permeability and reduced synthesis due to liver dysfunction (2). Furthermore, AT is considered as a negative acute-phase protein that is susceptible to enzymatic destruction by neutrophil proteases, such as elastase, released during post-burn systemic inflammatory states (17).

The magnitude of coagulation abnormalities in the early post-burn period, its relationship with organ failure and outcome, and the efficacy of the AT administration continue to be discussed in the literature.

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**Table 1: Main clinical and biological characteristics of the patients.**

	AT treated (n=15)	Non-AT treated (n=16)
Age (years)	37.1 ± 13.6	44.1 ± 21.5
Gender (% male)	80%	75%
TBSA (%)	43.3 ± 21.4	44.4 ± 22.4
ABSI	7.1 ± 2.2	7.7 ± 2.4
APACHE II score	12.7 ± 7	10.7 ± 4.3
SAPS II score	33.9 ± 10.6	37 ± 7.1
SOFA score	5.4 ± 1.6	4 ± 1.7
Inhalational burn (%)	26.6	31.3

No statistical significant differences were observed in any of above parameters.

The aim of this prospective study was to evaluate the early activation of coagulation after severe burn injury, to correlate the coagulation status alterations with prognosis and to estimate the effect of AT administration on coagulation parameters, organ failure and mortality.

## Materials and methods

Thirty-one patients with severe burn injury admitted to the four-bed Burn Unit in Papanicolau General Hospital, Thessaloniki, Greece from April 2004 to December 2005 were evaluated. Patients were randomly assigned into two groups: AT-treated and non-AT-treated groups using a sequence of randomly generated zero and ones according to SPSS 14 statistical software. The study protocol was approved by the local ethics committee, and written consent was obtained by the patients or their closest relatives.

All patients enrolled in the study during the first 24 hours after the burn injury. Patients with known haematological dis-

ease, hepatic and renal failure, malignancies and associated trauma were excluded from the study (n=5). AT administration was started from the 1<sup>st</sup> post-burn day and continued for the next three consecutive days at a dose of 64.9 ± 11.4 U/kg/day. The AT dose was titrated depending on the desired target value of plasma AT activity >150%. Each dose of AT was determined by the following formula: unit required (IU) = [(desired AT level-baseline AT level) × patients weight in kg] ÷ 1.4.

Patients' clinical management was guided by the written treatment protocol of our intensive care unit (ICU).

Anthropometric characteristics (age, sex) were recorded. Severity of the burn injury was estimated by the percentage of total burn surface area (TBSA) and the Abbreviated Burn Severity Index (ABSI). The severity of the illness was determined by the APACHE II score (Acute Physiology and Chronic Health Evaluation II) and SAPS II score (Simplified Acute Physiological Score II). For the diagnosis of multiple organ dysfunction or failure, the Sequential Organ Failure Assessment score (SOFA) was used. DIC score has been validated according to the International Society on Thrombosis and Haemostasis (ISTH) definition (18), and compared to the 28<sup>th</sup> day mortality. The following coagulation parameters were evaluated on ICU admission and thereafter daily for four consecutive days:

### Coagulation inhibitors

AT and protein C (PC) activities were measured in the plasma by chromogenic assay (Dade- Bering; normal values: AT range 80–120%, PC range 70–130%). The free protein S levels (PS) were also measured by electroimmunodiffusion method (Dade-Bering; normal values 70–130%).

### Factors of the fibrinolytic system

The plasminogen activator inhibitor 1 (PAI-1) and tissue plasminogen activator (t-PA) antigens were measured by the microenzyme-linked immunosorbent assay (ELISA) technique (Diagnostica Stago), (normal values 4–43 ng/ml for PAI-1, 1–12 ng/ml for t-PA).

**Table 2: Coagulation markers in early post-burn period in AT-treated and control groups.**

Parameter	AT treated		Non-AT treated	
	1 <sup>st</sup> day	4 <sup>th</sup> day	1 <sup>st</sup> day	4 <sup>th</sup> day
t-PA (ng/ml)	11.8 ± 1.8	5.9 ± 1.1*	8.8 ± 1.8	7.6 ± 1.2
PAI-1 (ng/ml)	52.4 ± 11.7	22.7 ± 4.8*	51.2 ± 12	34.3 ± 5*
TAT (µg/l)	11.6 ± 1.9	4.1 ± 1.7*	10.4 ± 1.9	9.4 ± 1.7
PAP (µg/l)	558.5 ± 58.5	505.4 ± 58.9	621 ± 60.7	659.8 ± 61.1
FI.2 (nM)	1.9 ± 0.5	1.2 ± 0.2*	2.6 ± 0.6	1.4 ± 0.4*
D-dimer (µg/ml)	2.0 ± 0.4	1.3 ± 0.3*	1.7 ± 0.3	2.5 ± 0.3*
Protein C (%)	59.9 ± 11	66.1 ± 18.8	70.6 ± 22	73.8 ± 28.5
Free protein S (%)	40.1 ± 12	58.8 ± 24.1	49.4 ± 20	62.7 ± 26.9
Platelets (10 <sup>9</sup> /l)	218.7 ± 77	134.8 ± 52*	250.7 ± 102	117 ± 51.3*
INR	1.4 ± 0.4	1.1 ± 0.2	1.27 ± 0.4	1.12 ± 0.2
APTT (s)	38.6 ± 15	36.4 ± 5.2	36.8 ± 9	35.7 ± 5.6

\*p<0.05 compared to 1<sup>st</sup> day. INR, international normalised ratio.

	D <sub>1</sub> (admission levels)	D <sub>2</sub>	D <sub>3</sub>	D <sub>4</sub>
AT-treated	44.3 ± 16	98.7 ± 15*	126.7 ± 21*	121.2 ± 18*
Non-AT-treated	54.7 ± 26	65.8 ± 13	71.2 ± 12	70.4 ± 19

D= day. \*p<0.05, AT- treated patients vs. control patients.

**Table 3: Time course of plasma AT concentration (%).**

### Activation of thrombin generation, fibrinolytic system and use of the coagulation inhibitors

The following markers were measured: thrombin / antithrombin complexes (TAT), plasmin /  $\alpha_2$ -antiplasmin complexes (PAP), prothrombin fragment F1+2 (F1+2) and fibrin degradation product D-dimer. TAT and PAP were measured by micro-ELISA assay (normal values 1–4.1  $\mu\text{g/l}$  for TAT, 120–700  $\mu\text{g/l}$  for PAP). D-dimer was measured by a latex semi-quantitative method (Diagnostica Stago; normal values: < 0.5  $\mu\text{g/ml}$ ). The F1+2 antigen levels were measured by the enzyme-linked immunoassay (normal values 0.4–1.1 nM).

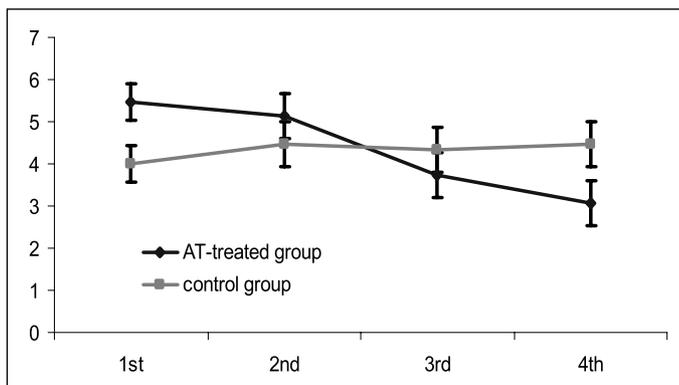
The patients' mortality was recorded on the 28<sup>th</sup> day of the ICU admission.

### Statistical analysis

ANOVA test was conducted for continuous variable measurements over time. Logistic regression analysis was used to evaluate the prognostic influence of DIC on the mortality rate and the corresponding odds ratios (OR) were calculated. Results were considered statistically significant for p-values less than 0.05. Statistical analysis was conducted with SPSS 14.0. Kaplan-Meier survival trend was used and the statistically significant difference was evaluated according to the Log Rank (Mantel-Cox) test between AT-treated and non-AT-treated groups. Values are expressed as mean  $\pm$  standard error of the mean (SEM).

## Results

The clinical and biological characteristics of the patients in the AT-treated group and in the non-AT-treated group are summarized in Table 1. The levels of coagulation system markers did not differ significantly between the two groups of patients on admission (Table 2).



**Figure 1: SOFA score of patients during the investigation period.**

Nine patients (29 %) fulfilled the overt DIC criteria, and 19 (61.3 %) the non-overt DIC on admission. Only a small number of survivors (three) did not fulfil the DIC criteria. In the AT-treated group five out of 15 patients fulfilled the overt DIC criteria and eight the non-overt DIC criteria. From the non-AT-treated group four patients had overt DIC diagnosis and 11 had non-overt DIC diagnosis.

Logistic regression analysis revealed that the presence of overt DIC is significantly related to death ( $b=2.303$ ,  $\text{SEM}=0.606$ ,  $p<0.001$ ,  $\text{OR}=10$ , 95% confidence interval [CI] = 3.23–32.26).

On admission, all patients had severe acquired deficiency of AT, PC and PS. A statistically significant increase of AT levels was observed in the treated group as compared to the non-AT-treated group,  $p<0.05$  (Table 3).

The coagulation markers at the 1<sup>st</sup> and 4<sup>th</sup> post-burn days are shown in Table 2.

The t-PA levels were within the physiological range in both groups of patients on admission and were decreased significantly on day 4 as compared to day 1 values only in the AT-treated group.

PAI-1 was increased above the physiological levels on day 1 after burn injury both in the non-AT-treated and in the AT-treated group. There was a statistically significant decrease of PAI-I levels in both groups from the 1<sup>st</sup> to the 4<sup>th</sup> day.

TAT levels were above the physiological range during the investigation period in both groups of patients, but significantly decreased in the AT treated groups from day one to day four.

PAP levels were within a physiological range (upper physiological levels) in both groups, while no statistically significant difference was observed between the two groups.

F1+2 levels were elevated on admission and decreased significantly in both groups from day 1 to day 4.

Both groups had high D-dimer levels in the early post-burn period, but a statistically significant decrease in the treatment group as compared to non-AT treated group was observed from day 1 to day 4.

AT-treated patients showed a decrease in SOFA score on day 3 and day 4 compared to the SOFA on admission. On the contrary, the non-AT-treated group patients did not change their SOFA score in the same period (Fig. 1).

By day 28, four out of 16 patients had died in the non-AT-treated group but no one in the treatment group. The main causative factor of death was the multi-organ failure syndrome, one non-survivor developed severe sepsis due to multi-drug resistant *Pseudomonas aeruginosa*. The non-survivors died on  $14 \pm 6.2$  day. Kaplan-Meier survival functions on day 28 showed a significant difference between the AT-treated and non-AT-treated patients [Chi-square = 8.227,  $p=0.004$ , Log rank (Mantel-Cox)

test]. None of the patients who received AT showed haemorrhagic complications.

## Discussion

The coagulation system homeostasis is frequently affected in burn patients (6, 19). While controlled activation of the coagulation system is an essential part of the wound healing process, uncontrolled activation of coagulation mediators, often seen in burn patients with severe injury, leads to increased morbidity and mortality. The hypercoagulable state of burn patients has been quoted as a main causative factor for DIC (6, 20).

Our study revealed that a high percentage of ICU burn patients (28 of 31) fulfilled DIC diagnosis criteria (9 overt and 19 non-overt). Only three survivors did not meet these criteria. DIC diagnosis seems to independently affect the mortality of burn patients.

Prior clinical studies indicated that in the early post-burn period the levels of coagulation inhibitors decreased and the levels of TAT, PAP, t-PA, PAI-1 and D-d increased (1–3, 6). A recent study of Niedermayr et al. (2) showed that 108 out of 201 patients developed AT plasma activity below 70% during their hospitalization.

We observed a significant alteration in the coagulation status early after the burn injury. AT levels decreased in all patients on admission. TAT levels were significantly elevated in all patients but decreased in the AT-treated patients on day 4. In agreement with others, we proved that the combined decrease in AT and consistently high levels in TAT in the non-AT-treated group indicate the increased consumption of coagulation inhibitors and augmented thrombogenicity (1, 3).

Increased levels of t-PA and the counterbalancing of its effect by increased levels of PAI-1 have been documented in sepsis and burn patients (1, 21). In sepsis patients, the t-PA and PAI-1 levels are higher in non-survivors and tend to normalize in survivors (22, 23). We observed moderate elevation of PAI-1 levels in contrast to the physiological levels of t-PA in both groups on admission. The t-PA levels decreased significantly on day 4 as compared to day 1 values in the AT treatment group of patients. On the contrary, the t-PA levels did not change significantly in the non-AT-treated group. In sepsis and burn patients, the t-PA levels were found to be higher in non-survivors and tend to normalize in survivors (3, 23). Decrease of t-PA may be explained by the diminishing of coagulation status abnormalities in the AT treatment group.

PAP levels were in the upper physiological ranges in both groups and did not change during the study period. This finding may indicate the overall inhibition of the fibrinolytic system in the early post-burn period. Some evidence existed in literature about PAP levels in ICU patients. In thermal injury patients Kowal-Vern et al. (24) found an elevated TAT / PAP ratio on day 1 which was decreased on day 5. Authors suggest that in the early post-burn period proportionately greater coagulation activation is observed as compared to fibrinolysis activation. Asakura et al. (25) reported that critically ill patients with DIC and multi-organ failure (MOF) had depressed levels of plasmin-antiplasmin than did those without MOF due to less fibrinolytic enhancement of DIC patients with MOF.

The increase in PAI-1 can be explained by the behaviour of PAI-1 as an acute-phase reactant in response to injury stress. Aoki et al. reported that the increase in PAI-1 was more rapid than the increase in fibrinogen or C-reactive protein in postoperative patients, suggesting that the PAI-1 level may be a sensitive indicator of the acute response to stress (26). On the other hand, the production of excess PAI-1 in the early phase of burn injury may play an important role in the development of hypercoagulability and organ dysfunction. Increased production of PAI-1 combined with physiological levels of t-PA, observed in our study, may indicate hypofibrinolytic status in the early post-burn period.

Our observations are in accordance with the findings of Watanabe et al. (27) in septic patients with DIC. In this study it is suggested that the increased fibrin formation in association with impaired fibrinolysis may promote DIC and contribute to both organ damage and mortality.

Elevated D-dimer levels *per se* have been shown to have a negative impact on survival in patients with severe sepsis and DIC, presumably as a reflection of the ongoing and unopposed activation of coagulation and consumption of pro-coagulant factors (28). The elevated plasma concentrations of D-dimer and F1+2 found in our patients are reflected in an increased generation of plasmin and an overall activation of the fibrinolytic system. A different time-trend of D-dimer was found in the two groups: a decrease in the AT-treated group and an increase in the non-AT-treated group. Our results are in agreement with Kountchev et al. (29) who investigated the changes in circulating levels of D-dimer in response to the administration of AT in sepsis patients. Six hours after AT administration significant decrease in D-dimer levels from  $3,254 \pm 1,053 \mu\text{g/l}$  to  $2,388 \pm 2,014 \mu\text{g/l}$  ( $p=0.028$ ) was observed, corresponding to a  $26.7 \pm 5.7\%$  reduction of D-dimer levels.

Several clinical studies report the efficacy of AT supplementation in different clinical situations is associated with acquired deficiency in coagulation inhibitors (30–34). In a recent placebo-controlled multicenter trial (KyberSept trial) (35), which tested the influence of high-dosage AT therapy in more than 2,300 patients with severe sepsis, AT reduced mortality only in the subgroup of patients who did not concomitantly receive heparin during the four-day treatment period. In our study a statistically significant decrease in 28<sup>th</sup> day mortality was also observed in the AT treatment group ( $p=0.04$ ).

In burn patients a favourable effect of AT supplementation on organ dysfunction has been reported in some clinical and experimental reports (1, 8–10), but we were unable to find a controlled clinical study in the literature.

The primary objective of our study was to evaluate the potential benefit of AT treatment in preventing major organ dysfunction (according to SOFA score) and mortality. SOFA score is the most commonly used scoring system for the evaluation of organ dysfunction and failure in critically ill patients over the course of their ICU state. It is composed of scores from six organ systems (respiratory, coagulation, cardiovascular, hepatic, and renal and central nervous system). A statistically significant difference in the time-trend of SOFA score was observed between the AT-treated and the non-AT-treated group ( $p<0.001$ ). The SOFA score decreased in the AT-treated group, but remained unchanged in the non-AT-treated group.

AT administration was well tolerated in our patients, and none of our patients had haemorrhagic complications during the study period. It is reported that treatment with AT has a modest effect on the incidence of major bleeding events (10). Kienast et al. found in AT-treated septic patients that the absolute increase of major bleeding was 1.8% in DIC patients compared to 6.7% in patients without DIC (35). Thus, the increase in the risk of major bleeding appeared to remain relatively low for AT-treated patients, at least in the presence of DIC.

## Conclusion

Activation of coagulation mediators was detected in ICU patients with severe burn injury and most of these patients fulfilled the criteria of DIC syndrome. The diagnosis of DIC was related to mortality. Treatment with AT seems to decrease the state of hypercoagulation in these patients (decreased TAT and D-dimer). Improvement of organ function was observed in patients after AT administration.

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