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EVALUATION OF ANTITHROMBIN- III IN MULTIPLE TRAUMATIC PATIENTS WITH TRAUMA SCORES IN THE EMERGENCY DEPARTMENT

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Abstract
Purpose: In this prospective study, we aimed to show how trauma severity and posttraumatic time effect some blood parameters such as anti-thrombin III (AT-III), blood thrombocyte count, active partial thromboplastine time (aPTT), prothrombin time (PT), and fibrinogen level.

Methods: Thirty patients with multiple trauma admitted to Dicle University Hospital, department of emergency between January 1998-March 1999 were evaluated. Bloods were taken intravenously from all patients at admission and third posttraumatic days for evaluating parameters. Patients were divided into 3 groups according to injury severity score (ISS) and Glasgow Coma Score (GCS):

Group 1- patients (n=8) with severe multiple trauma and severe head trauma (ISS>25, GCS<8); Group 2- patients (n=8) with severe trauma and mild head trauma (ISS >25, GCS>12); Group 3- patients (n=14) with mild multiple trauma and mild head trauma (ISS <25, GCS>12). Statistical analysis was done with SPSS 6.0 software.

Results: Anti-thrombin III level was lower in-group 2 (high ISS) when compared to group 1 and 3 (p=0.007). Although AT-III level in group 2 was little but increased at 3rd day, it was still lower than group 1 and 3. Anti-thrombin levels of groups at admission and 3rd days were as follows: 32.3±11.5 mg/dl and 35±27.9 in group 1; 26.7± 8.1 mg/dl, 30.8± 11.8 mg/dl in group 2; 39.7± 8.9 mg/dl, 39.3±14.6 mg/dl in-group 3. No statistical differences were found in APTT, thrombocyte counts of groups (p>0.05). Prothrombin time was decreased at 3rd day when all patients were examined (p=0.0006). Although fibrinogens were in the normal levels in all groups, in-group 2 it was higher at admission when compared to other groups (p=0.02), no different was at 3rd day (p>0.05).

Conclusion: As a conclusion, AT-III level decrease with severity of trauma. This may increase the risk of thrombo-emboli phenomena in multiple trauma patients.

Introduction

Patients with multiple traumas are the patients that need to be evaluated quickly in the Emergency Services. Because they have different injuries that fall into the interest areas of different branches, the injury and the trauma needs to be scored and first aid principles should be applied. The scoring systems that are developed according to recent developments in medical science, help the quick and suitable triage of patients with multiple traumas to which transportation, first aid, resuscitation and treatment will be applied [4].

Many studies show that transportation of the injured patients to a health center that has limited opportunities, and the application of insufficient and time-wasting treatments to these patients, leads to higher than expected mortality rates [18]. Another important problem for patients with multiple trauma is the risk of thrombo-emboli which increases with the age and the severity of the patients' trauma. The importance of Anti-thrombin III (AT-III) on thrombo-emboli should also be emphasized [7]. AT-III is the main plasma protein responsible for the progressive inactivation of thrombin. The AT-III activity may decrease because of some pathological reasons. They are: 1) the absorption of thrombin on fibrin, 2) fibrinogen activity and the existence of fibrin destruction products, 3) the existence of cavalier heparin with the exception of the known plasma proteins known as heparin cofactor. One of the most important factors of the creation of thrombosis inside the vein is the hypercoagulability of the blood. If there is a decrease in AT-III in the blood, this increases the risk of intravascular coagulation as blood is apt to coagulate and

form thromboembolisms with a resultant increase in the incidence of atherosclerosis. Excess lipids in the blood cause hypercoagulability by inhibiting fibrinolytic activity [5,7,8,18].

It is observed that publications on studies of the risk of thrombo-emboli and AT-III and other hematological parameters on patients with multiple trauma is needed in our country. In this study, we aim to show how trauma severity and post-trauma time effect some blood parameters such as AT-III, blood thrombocyte count, active partial thromboplastine time (aPTT), prothrombin time (PT) and fibrinogen level.

Materials and Methods

In this prospective study, thirty patients admitted to Dicle University Hospital, Department of Emergency between January 1998 - March 1999 with multiple trauma were evaluated. Patients were scored according to the Injury Severe Score (ISS) and Glasgow Coma Score (GCS) (Table 1,2). Abbreviated Injury Scale (AIS) and the injuries in the whole body systems are evaluated in calculating ISS. The ISS has six parameters with points ranging from 0 to 5. The lowest score is 0 and the highest score is 30. ISS is evaluated by the addition of the squares of the highest three AIS values. The score is in the range of 1 to 75. It is directly proportional with the mortality. For GCS; 3 is the worst score while 15 is the best one. A score of 8 or lower, corresponds to coma or severe head trauma; if the score is 9 to 12, head trauma with medium severity is indicated; if the score is 13 or higher, mild head trauma is assumed. [4,18].

The patients were divided into 3 groups according to their ISS and GCS scores:

- Group I: patients (n=8) with severe multiple trauma and severe head trauma (ISS>25, GCS<8),
- Group II: patients (n=8) with severe trauma and mild head trauma (ISS>25, GCS>12),
- Group III: patients (n=14) with mild multiple trauma and mild head trauma (ISS<25, GCS>12).

After the initial examination, their respiratory and circulatory systems were examined and intubations and liquid replacement (for the patients who lose volume) were applied when needed. Full blood examinations, biochemical examinations, ECG and cranial tomography (for some cases) were done. The patients that needed to have surgical treatment were taken to the appropriate services of the hospital and continued to be followed.

Blood for test would be based to evaluation were taken intravenously from all patients at admission and three days post-trauma and also full blood with EDTA (1.8 ml, EDTA (K3); Becton Dickinson Vacutainer Systems, France) and into the PT tubes (3 ml, CIT.No-0.129M, SILIC.; Becton Dickinson Vacutainer Systems, France). They were studied by centrifuging for 10 minutes at 10000cyc/min at 2-8°C in the Central Laboratory.

The level of plasma AT-III was evaluated by using Beckman AT-III diagnostic test and Beckman Array 360 System Nephelometric Centrifugal Analyzer (The components of the test are the AT-III anticore and the AT-III anticore card. Human AT-III anticore and 0.1% (w/v) sodium aside were used as conservator in 5ml of AT-III anticore.). The lower boundary for the evaluation was <5 mg/dl. The normal values (for the tubes with EDTA) are 27.7 - 38.3 mg/dl.

PT and fibrinogen level were evaluated by using the IL TEST PT-FIBRINOGEN (Instrumentation Laboratory SpA-Italy) diagnostic test and the Nephelometric method. Normal values for the PT is 10.7 - 13.0" (140 - 70%) while that of fibrinogen is 200 - 400 mg/dl. aPTT was evaluated by using the IL APTT (Instrumentation Laboratory SpA-Italy) diagnostic test and the Nephelometric method. Normal value for the aPTT is 27 - 35". Cross-reference tables were prepared by evaluating the AT-III, fibrinogen, aPTT and PT levels according to the severity of the trauma for the patients with multiple trauma.

Table 1. Glasgow Coma Score.

	Injury	Score
Motor Response	Can do as he/she is told	6
	Localization of pain	5
	Pull response to pain	4
	Flexion response to pain	3
	Extension response to pain	2
	No response	1
Verbal Response	Fully conscious	5
	Conscious but blurred	4
	Nonsense words	3
	Nonsense voices	2
	No response	1
Condition of eyes	Spontaneously open	4
	Opens in response to voice	3
	Opens in response to pain	2
	Continuously closed	1

Table 2. AIS (Abbreviated Injury Scale).

	Injury	Score

Head-Neck	No injury	0
	Mild injury	1
	Medium level injury	2
	Severe injury, but no life risk	3
	Severe injury, life risk	4
	Critical	5
Skin	No injury	0
	Mild injury	1
	Medium level injury	2
	Severe injury, but no life risk	3
	Severe injury, life risk	4
	Critical	5
Face	No injury	0
	Mild injury	1
	Medium level injury	2
	Severe injury, but no life risk	3
	Severe injury, life risk	4
	Critical	5
Thorax	No injury	0
	Mild injury	1
	Medium level injury	2
	Severe injury, but no life risk	3
	Severe injury, life risk	4
	Critical	5
Abdomen	No injury	0
	Mild injury	1
	Medium level injury	2
	Severe injury, but no life risk	3
	Severe injury, life risk	4
	Critical	5
Extremities	No injury	0
	Mild injury	1
	Medium level injury	2
	Severe injury, but no life risk	3
	Severe injury, life risk	4

	Critical	5

Statistical Analysis

Statistical analysis of the study was done by using the SPSS 6.0 software. For the comparison of two matched groups, Wilcoxon Matched-Pairs Signed-Ranks Test; for the unmatched samples, non-parametric Mann-Whitney U test; for the comparison of multiple invariant samples, Variance Analysis, One-way ANOVA, Multiple Range Test, Modified LSD (Bonferroni) Test; for the comparison of categorical variables, χ^2; for the correlation analysis, Pearson Correlation Test; for the linear relationships, Multiple Regression Analysis were used. $P<0.05$ was considered to be significant.

Results

When we evaluate the demographic data for our patient group, we observe that the mean age for the 30 patients is 25±19, while the range is 4 - 74 years (Table 3). 24 of them are men and 6 of them are women, while men/women ratio is 4/1. 33.3% of them are between 0 - 14 years of age, 53.3% of them are between 14 - 20 years of age 80% of them are between 20 - 35 years of age. Most of the patients were treated and chased in the Emergency (n: 13) and Brain Surgery (n: 11) Services; while the others were chased in the General Surgery (n: 4), Orthopedics (n: 1) and Pediatric Surgery (n: 1) Services (Table 3).

Table 3. General Sociodemographic Data of the Patients.

	Group I (n)	*Group II* (n)	*Group III* (n)	*Total* (n)
City where the patient came from				
Diyarbakır	5	3	9	17
Şanlıurfa	-	1	1	2
Mardin	1	3	3	7
Batman	2	1	1	4
Reason of Trauma				
Injury by gun	-	-	1	1
Traffic accident	7	6	7	20
Crumble	1	1	4	6
Others	-	1	2	3
Service in the Hospital				
Emergency	2	6	5	13
Brain Surgery	5	1	5	11
General Surgery	1	1	2	4
Orthopedia	-	-	1	1
Pediatric Surgery	-	-	1	1
Exitus/Alive				
Exitus	2	-	1	3
Alive	6	8	13	27
Reason of Exitus				
Intracranial bleeding	2	-	-	2
Postoperative complication	-	-	1	1
Gender				
Male	7	6	11	24
Female	1	2	3	6
Total	8	8	14	30

The first two of the three patient that had been exitus, among the total of 30 patients, were the patients that were taken to the Brain Surgery Service and they had been exitus because of intra cranial bleeding. They were 12 and 70 years old. Their ISS values were 25 and 39, while GCS of were 8 and 5 respectively. The third patient that had been exitus was a 35 year old man who was in Group III and had been exitus on the first day postoperatively while he was in the Orthopedia Service. His ISS score was 22, GCS score was 15 and the other hematological parameters were normal. All three patients were taken to the Emergency Service 120 minutes after being exitus (Table 4).

Table 4. Trauma Scores, Ages and Time Taken to Attempt the Emergency Service of the Patients According to the Groups.

	Group I	*Group II*	*Group III*	*P*
GLASGOW	**6±1**	**14±2**	**15±1**	**> 0.0001**
ISS	**38±9**	**37±6**	**15±6**	**> 0.0001**
Time (minutes)	**146±66**	**341±423**	**390±351**	**> 0.05**
Age (years)	**19.7±20.9**	**26.5±12.6**	**27.7±21.9**	**> 0.05**

Most of the trauma reasons of the patients were traffic accident (n: 20). More than half of them came from Diyarbakir (n: 17). The rest of them came from the surrounding cities of Diyarbakir (Sanliurfa, Mardin, Batman) (Table 3). The mean time that had taken to take them to the Emergency Service is 312±332 minutes (minimum of 30, maximum of 1080 minutes). 56.7% of the patients arrived at the hospital in the first 120 minutes. The percentage of the patients that arrived at the hospital in the first one hour is only 10.

On first day of the trauma, it was found to be a strong negative correlation between the AT-III level and the ISS score (r=0.49, P=0.005; Multiple Regression Analysis T=-3.9, P=0.005, Beta=-0.78, 95% CI=0.94; -0.29). But there was no correlation between the ISS and the first day fibrinogen, thrombocyte count, PT, aPTT and between the third day AT-III, fibrinogen, thrombocyte count, PT, aPTT levels and the Glasgow Coma score. Mean Glasgow score was 12±4 and the ISS score was 27±14. Intravenous liquid was not applied to the 11 patients before attempting to the Emergency Service, while at least 500ml of IV liquid was given to the 19 patients before attempting to the Emergency Service.

There was no significant difference between the hematological parameters of the patients except PT (Table 5). When the hematological parameters were compared in accordance with the group base, it was observed that AT-III levels of Group II patients were lower than that of Group I and III patients (Table 6). When the admission and the third posttraumatic day parameter levels were compared, it was observed that AT-III level was

low on the admission day for the Group I and II patients, while it had increased on the third posttraumatic day (Table 7).

Table 5. Comparison of Hematological Parameters of the Patients.

	Day 0 ***(Mean±SD)***	***Day 3*** ***(Mean±SD)***	***P****
AT-III (mg/dl)	34.2±10.7	35.7±17.9	>0.05
aPTT (″)	26.7±6.4	23.1±9.2	>0.05
Fibrinogen (mg/dl)	261±8.5	308±15.5	>0.05
PT (″)	13.1±1.4	10.6±3.9	=0.0006
Thrombocyte count (X1000/mm^3)	260±88	220±107	>0.05

**Wilcoxon Matched-Pairs Signed-Ranks Test*

Table 6. Comparison of hematological parameters of the patients according to Groups.

	Group I		**Group II**		**Group III**	
	Day 0	***Day 3***	***Day 0***	***Day 3***	***Day 0***	***Day 3***
AT-III (mg/dl)	32.3±11.5	35.2±27.9	26.7±8.1	30.8±11.8	39.7±8.9	39.3±14.6
aPTT (″)	28.5±10.1	16.5±11.9	24.2±2.7	27.1±3.9	27.2±5.2	24.3±8.5
Fibrinogen (mg/dl)	225±77	278±194	330±61	359±124	241±82	291±153
PT (″)	13.7±1.7	8.7±5.6	12.4±1.1	12.2±0.6	13.2±1.4	11.1±3.6
Thrombocyte count (X1000/mm^3)	274±96	191±150	220±85	213±60	274±85	240±105

Table 7. Compared of first day (date of event) and 3rd day hematological parameters of groups.

	Group I	**Group II**	**Group III**	**P**
APTT (")				

First Day 3rd Day	28.5±10.1 16.5±11.9	24.2±2.7 27.1±3.9	27.2±5.2 24.3±8.5	>0.05 >0.05
AT-III (mg/dl) First Day 3rd Day	32.3±11.5 35.2±27.9	26.7±8.1* 30.8±11.8	39.7± 8.9 39.3±14.6	=0.007 >0.05
Fibrinogen (mg/dl) First Day 3rd Day	225±77 278± 194	330±61** 359± 124	241±82 291±153	=0.02 >0.05
Throm-bocytes (x1000/mm^3) First Day 3 rd Day	274±96 191±150	220±85 213±60	274± 85 240± 105	>0.05 >0.05
PT (“) First Day 3 rd Day	13.7±1.7 8.1±5.6	12.4±1.1 12.2±0.6	13.2±1.4 11.1±3.6	>0.05 >0.05

*One-way ANOVA Multiple Range Tests: Modified LSD (Bonferroni) test 0.05 level.

* Group II was different. ** Group II was different.

Discussion

The studies that use ISS system on the AT-III, aPTT, PT, fibrinogen and thrombocyte levels in accordance with the severity of the trauma for the patients with multiple trauma report that ISS has a correlation with the lethality [5,8]. Studies show that ISS is an appropriate scoring system for evaluating patients with multiple trauma [9,13].

It was reported that, the risk of thrombo-emboli increases with the age and the severity of the trauma for the patients with multiple trauma [7,8,10]. It was shown by a study of Nast-Kolp *et al.* in Germany [11] that there is a relationship between the severity of the trauma and the AT-III level. It was shown by a study of Risberg *et al.* [16] on 20 patients with multiple trauma that the levels of AT-III and alpha-plasmine inhibitors decrease. In another study carried out by Erichsen *et al.* [17], this was also proved on 19 patients.

Also in our study, there was a strong negative linear correlation between the injury day AT-III level and the ISS score ($r=-0.49$, $p=0.005$, Beta=-0.78, 95% CI=-0.94;-0.29) . The injury day AT-III levels (39.7±8.9 mg/dl) of the patients with severe multiple trauma whose ISS scores were higher than 25 were lower than that of the patients with mild multiple trauma (39.7±8.9 mg/dl); but both of the levels were in the normal ranges ($p=0.006$, 95% CI=17.3;-3.2). For the same group, the fibrinogen level was found to be high on the injury day ($p=0.02$). There was no statistical difference between the other values. When all the groups are of our concern, there was no significant difference in the AT-III, aPTT, fibrinogen and thrombocyte levels between the 0th day and the 3rd day ($p>0.05$) while PT level decreased on the 3rd day ($p=0.0006$).

In a study carried out in Denmark by Sorensen *et al.* [20] , it was shown that isolated head trauma and multiple trauma might cause an increase the levels of Prothrombin fragment 1 & 2 (F 1+2) and thrombin /AT-III complex (TAT) which reflect the haemostatic activation. This study shows us that AT-III is used in complex forms for the patients with multiple trauma. Decreasing the AT-III level in our study is also due to the same reason. Furthermore, in Sorensen *et al.* [20], a better haemostatic response trend was achieved for the patients with multiple trauma compared to the patients with isolated head trauma.

This indicates that, a good haemostatic response causes the AT-III level to decrease, which also conforms to the results of our study. In the study of Sorensen *et al.* [20], F1+2 and TAT levels decrease day by day after the trauma. This means that AT-III should have been used less during the following days after the trauma and this shows us that AT-III levels would increase. A difference in the AT-III level had also been observed between day 0 and the 3rd day in our study. These results are also compatible with the study of Bick [2] and other studies by Sorensen *et al.* [19,21,22].

Sorensen and friends observed that, the TAT level was higher for patients with multiple trauma compared to the patients with head trauma [20]. This means that AT-III was used more for the patients with multiple trauma. The levels of AT-III was found to be low for Group II which comprises of patients with severe multiple trauma also in our study (Table 7). The F1+2 and TAT levels are also strongly related to the ISS scores for the first three days in the same study [20]. Also in our study, the AT-III levels decreased for the patients with high ISS scores.

Low AT-III, fibrinogen, high fibrinogen destruction products level and thrombocytopenia together with agency dysfunctions are generally considered as the diagnostic criteria for the disseminate intravascular coagulation (DIC) [2]. The monocytes and the injury macrophages system are activated during the first 24 - 72 hours after the injury [3,12]. The cytokines and the continuous coagulation activity by the procoagulan activity may also take part. It was reported that, the infusion of tumor necrotizing factor (TNF) causes the F1+2 levels to increase in the humans [1]. It was also reported that, DIC is a general complication of severe head trauma and multiple trauma [2,6,14,15,23]. This makes us think that, for these patients the coagulation system works harder which causes AT-III level to decrease.

As a result; it is concluded that, the risk of thrombo-emboli increases for the patients who attempts to the Emergency Service with multiple trauma, so their treatment should be planned accordingly.

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