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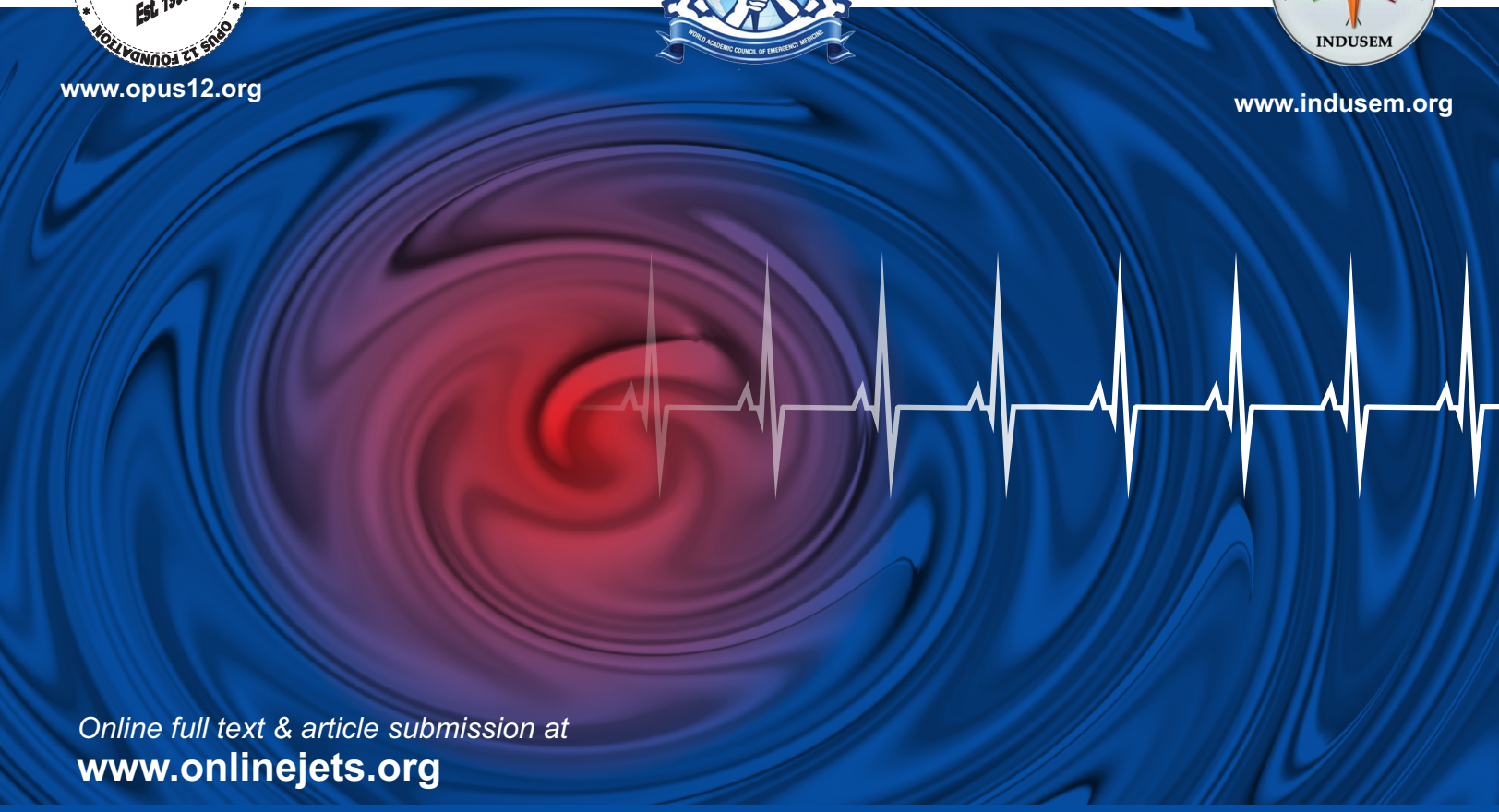

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Original Article

Increase in Fibrinogen Degradation Product Levels 5 Days after a Traumatic Insult

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Abstract

Context: Few reports have investigated the time course of fibrinogen (or fibrin) degradation product (FDP) levels for trauma patients in the subacute phase. **Aims:** This study aimed to investigate the time course of the FDP levels among patients with moderate and severe trauma in the subacute phase. **Settings and Design:** A retrospective medical chart review in a single hospital. **Subjects and Methods:** From September 2017 to March 2018, a medical chart review was retrospectively performed for all patients with trauma who were admitted to our department, and these patients were included as participants in the present study. We collected the data on each patient's sex, age, presence of head injury, mechanism of injury, Glasgow Coma Scale on arrival, systolic blood pressure, heart rate, type of injury (blunt versus penetrating), injury severity score, complication of infection, surgical procedure, duration of admission, survival rate, and FDP level from the 1st to 7th hospital day. The average level of FDP on each hospital day was compared with that on the previous day. **Statistical Analysis Used:** The statistical analyses were performed using a paired Student's *t*-test. $P < 0.05$ was considered to indicate a statistically significant difference. **Results:** From the 1st to 4th hospital day, the average level of FDP significantly diminished day by day. However, from the 5th hospital day, the average level significantly increased. This trend persisted even after excluding the complications of infection and surgical procedures performed between the 2nd and 7th hospital day. **Conclusions:** Among trauma patients, the average level of FDP significantly diminished day by day from the admission to the 4th hospital day; however, from the 5th hospital day, the average level significantly increased. Further studies are needed to determine the time course of FDP or D-dimer levels in the long term and when FDP levels return to normal limits.

Keywords: Fibrinogen degradation product, injury severity score, time course

Introduction

Fibrinogen (or fibrin) degradation products (FDPs) are fragments released following plasmin-mediated degradation of fibrinogen or fibrin.[1] The D-dimer is a specific fragment formed only upon the degradation of cross-linked fibrin. The activation of the coagulation cascade results in thrombin generation, which in turn cleaves fibrinogen to form fibrin monomers. Cross-linked fibrin is the end-point of the coagulation cascade. Plasmin, which is part of the fibrinolytic pathway, degrades fibrin and fibrinogen, resulting in FDPs.

As mentioned, D-dimer fragments are detected only upon the degradation of cross-linked fibrin, indicating active coagulation and fibrinolysis. The FDP or D-dimer level is very sensitive to intravascular thrombus and may be markedly elevated in cases of disseminated intravascular coagulation (DIC), acute aortic dissection, and pulmonary embolus.[2]

The tissue contains a tissue plasminogen activator, and when tissue is damaged by trauma, elevated FDP levels are recognized as a result of fibrinolysis due to the release of tissue plasminogen activator. For traumatized patients, the level of FDP on arrival has been reported to be a useful biochemical marker for predicting the severity and mortality.[3-5] FDP levels decrease rapidly after trauma impact in the acute phase; however, few reports have investigated

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the time course of FDP levels for trauma patients in the subacute phase.[6,7]

We, therefore, retrospectively analyzed trauma patients who were transported to our department to investigate the time course of the FDP level in the subacute phase.

Subjects and Methods

The protocol of this retrospective study was approved by the review board of Shizuoka Hospital, Juntendo University, and all examinations were conducted in accordance with the standards of good clinical practice and the Declaration of Helsinki.

Shizuoka Hospital, Juntendo University, which is a hospital with 577 beds and a medical emergency center in Eastern Shizuoka Prefecture located near Tokyo, serves a population of approximately 1,230,000. The helicopter parks at Juntendo Shizuoka Hospital, and the DH mainly treats patients with severe trauma, acute coronary syndrome, stroke, cardiopulmonary arrest, drowning, decompression sickness, intoxication, and unstable vital signs.

From September 2017 to March 2018, a medical chart review was retrospectively performed for all patients with trauma who were admitted to our department, and these patients were included as participants in the present study. The exclusion criterion was a lack of continuous data for FDP levels from the 1st to 5th hospital day. We collected the data on each patient's sex, age, presence of head injury, mechanism of injury, Glasgow Coma Scale on arrival, systolic blood pressure, heart rate, type of injury (blunt versus penetrating), number (rate) of head/chest/abdomen/pelvic/extremity/spine injuries which with an abbreviated injury scale exceeding 1, injury severity score, complications of infection, DIC, and multiple organ failure (MOF), surgical procedure, duration of admission, survival rate, and FDP level from the 1st to 7th hospital day. We also investigated the number of patients who underwent whole-body (head to upper thigh) enhanced computed tomography after hospital day 5, number of patients who underwent enhanced computed tomography and/or ultrasound sonography for screening of deep-venous thrombosis of the lower extremities, and number of patients who underwent anticoagulation therapy before hospital day 7, and also the number of thrombotic/embolic events during hospitalization. Infection was diagnosed in the present study based on the detection of a pathogen and an increase in inflammatory biomarkers, such as the white blood cell count or C-reactive protein or presepsin levels in the presence of clinical symptoms.[8,9] DIC was defined based on the scoring system of the Scientific and Standardization Committee on DIC.[10] DIC was diagnosed in cases with a score of ≥5. Severe organ failure was defined as a sequential organ failure assessment score of ≥3 in any organ system.[11] MOF was defined as the occurrence of severe organ failure in two or more organ systems during the patient's intensive care unit stay. The average level of FDP on each hospital day was compared with that from the previous day. We also investigated the correlation between the duration of admission and the FDP level on the 1st hospital day.

The statistical analyses were performed using a paired Student's *t*-test. $P < 0.05$ was considered to indicate a statistically significant difference. All the data are presented as the mean ± standard deviation.

Results

During the investigation period, a total of 907 patients were treated in our department. Among these patients, 453 were trauma cases, and 222 of these were admitted. Among them, 158 cases were admitted for more than 5 days. Of these, 118 lacked continuous measurements of the FDP level. After excluding these cases, the remaining 40 cases were enrolled as participants [Figure 1].

The background characteristics of the participants are shown in Table 1. The duration of admission was 20.2 adding 0.04* fibrinogen degradation product level on the 1st day. The correlation coefficient was 0.37 ($P = 0.01$).

The average and standard deviation of the FDP level from the 1st to 7th hospital day, and comparisons with the previous day are shown in Table 2 and Figures 2 and 3. From the 1st to 4th hospital day, the average level of FDP significantly diminished day by day. However, from the 5th hospital day, the average level significantly increased. This trend persisted even after excluding the complications of infection and surgical procedures performed between the 2nd and 7th hospital day [Table 3].

As the average of FDP level on the 5th hospital day was higher than that on the previous day, we further investigated the platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen on the 1st and 5th hospital days [Table 4]. The platelet count on the 5th hospital day significantly decreased in comparison to the 1st hospital day. However, no patients fulfilled the criteria for DIC on the 5th hospital day. In addition, no thrombotic/embolic events occurred in any of the analyzed patients during hospitalization.

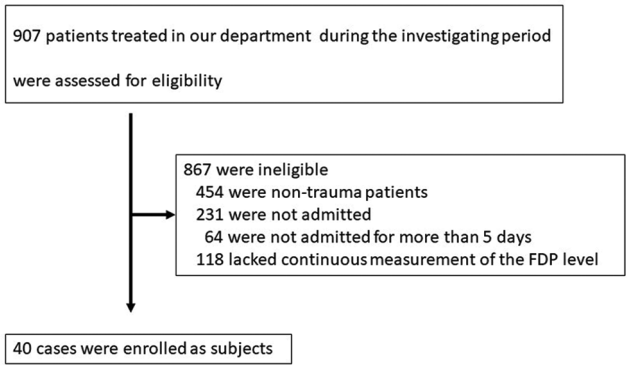

Figure 1: Flow diagram of the present study. Among 907 patients treated in our department, 40 cases were enrolled as participants

Table 1: Background characteristics of participants

Variables	Results
Sex (male/female)	29/11
Age (years)	64.1±18.7
Mechanism: Blunt/penetrating	39/1
Traumatic lesion in total (abbreviated injury scale >2) (%)	
Head	10 (25)
Chest	22 (55)
Abdomen	11 (27.5)
Pelvis	15 (37.5)
Spine	15 (37.5)
Extremity	19 (47.5)
Systolic blood pressure (mmHg)	118.7±30.1
Heart rate (beats/min)	85.5±19.9
Glasgow coma scale	14 (14–15)
Injury severity score	15.7±7.1
Complication of infection (%)	12 (30)
Surgical management on the 1st hospital day (%)	20 (50)
Surgical management after the 1st hospital day (%)	6 (15)
Enhanced whole-body computed tomography after hospital day 5 (%)	17 (42.5)
Enhanced computed tomography and/or ultrasound sonography for the screening of deep-venous thrombosis of the lower extremity (%)	2 (5)
Anticoagulation therapy before hospital day 7 (%)	3 (6)
Duration of admission (day)	27.5±23.1
Survival ratio (%)	100

Table 2: Time course of fibrinogen degradation product level (μg/ml) among all participants

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
n	40	40	40	40	40	19	4
Mean±SD	187±224	47±62	15±14	12±9	18±11	28±20	23±19
n	<0.0001	<0.001	<0.05	<0.0001	0.01	NS	

Each FDP level on a given day is compared with that on the previous day. SD: Standard deviation, FDP: Fibrinogen degradation product, NS: Not significant

Table 3: Time course of fibrinogen degradation product level (μg/ml) excluding surgical procedures after the 1st hospital day and complications of infection

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
n	21	21	21	21	21	9	2
Mean±SD	203±234	36±31	12±10	10±5	16±10	18±5	29±31
P	<0.01	<0.001	<0.05	<0.001	<0.05		

Each FDP level on a given day is compared with that on the previous day. SD: Standard deviation, FDP: Fibrinogen degradation product

Discussion

This is the first study to demonstrate that, among trauma patients, the average level of FDP significantly diminished day by day from admission to the 4th hospital day; however, from the 5th hospital day, the average level significantly increased, even after excluding the complications of infection and surgical procedures.

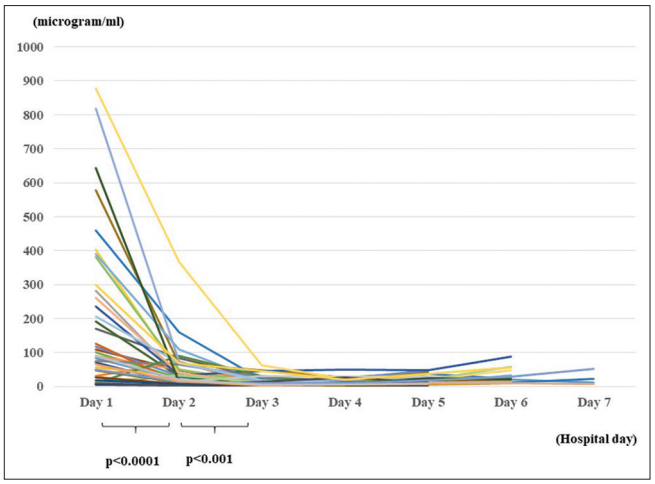

Figure 2: The time course of the fibrinogen (or fibrin) degradation product level in each participant. The average fibrinogen (or fibrin) degradation product level on the 2nd and 3rd hospital day was significantly lower than on respective previous days

Three previous reports have described the time course of FDP or D-dimer levels among traumatized patients. Nakae *et al*. reported the time course of D-dimer levels at 1, 3, 6, and 12 h after injury among patients with isolated traumatic brain injury.[6] Elevated D-dimer levels on admission decreased hour by hour. However, those authors only evaluated the time course of D-dimer levels on the 1st day. Gando *et al*. reported the time course of D-dimer levels at 1, 2, 3, and 4 days after admission among traumatized patients with and without head injury.[7] They showed markedly elevated D-dimer levels on the day of admission, which then gradually decreased to day 4. In addition, the levels and the time course of hemostatic markers (tissue factor antigen concentration, prothrombin fragment F1 + 2, thrombin antithrombin complex, and fibrinopeptide A in addition to D-dimer) in patients with isolated head injury were not markedly different from those without head injury. Until the 4th hospital day, their results were similar to our own, but they did not evaluate the findings on the 5th day or later. Sørensen *et al*. measured the FDP level on days 1, 2, 3, and 7.[10] They found that the FDP level decreased until the 3rd day but was significantly higher on day 7 than on day 3. Accordingly, they also showed an increasing trend in the FDP level after the 5th hospital day, similar to our own findings. However, they did not suggest any mechanism that might underlie the increase in the FDP level on the 7th day. As the FDP level was measured on the 7th hospital day in only four participants in the present study, we were unable to show any significant difference in the FDP level between the 3rd and 7th day.

Among traumatized patients, a decreasing FDP level from admission to the 4th day suggests a decreasing release of tissue plasminogen activator from damaged tissue and/or decreasing formation of clot and thrombus at the damaged tissue. However, three possible mechanisms may underlie the increase in the FDP level from the 5th hospital day. The

Table 4: Comparison of the platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, and fibrinogen degradation product between the 1st and 5th hospital days

	Day 1	Day 5	*P*
Platelet count (×10⁴/mm³)	19.3±6.5	14.7±7.4	<0.0001
Prothrombin time (s)	11.9±1.3	12.2±2.9	NS
Activated partial thromboplastin time (s)	27.7±4.1	30.3±11.2	NS
Fibrinogen (mg/dl)	246.4±92.1	491.1±150.7	<0.0001
FDP level (μg/ml)	187.3±224.0	18.9±11.8	<0.0001

NS: Not significant, FDP: Fibrinogen degradation product

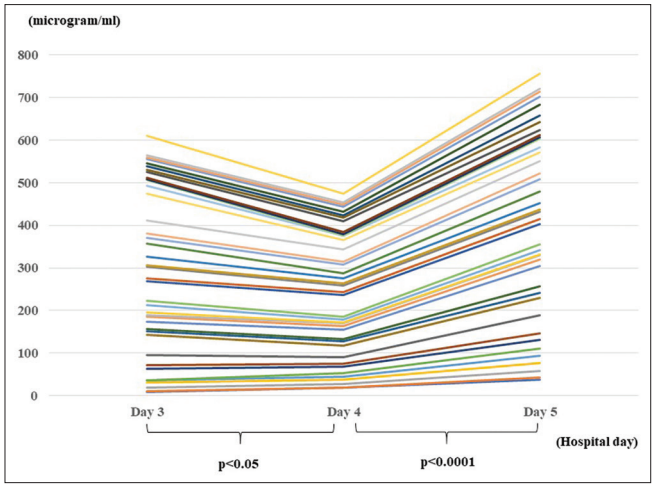

Figure 3: The average level of fibrinogen (or fibrin) degradation product was significantly lower on the 4th hospital day compared with the 3rd; however, the average level on the 5th hospital day was significantly higher than on the 4th

first possible mechanism is the complication of deep-venous thrombosis, as requiring admission for over 5 days suggests more than mild trauma, so bed rest may be required. Bed rest is one risk factor of deep-venous thrombosis, even though all participants in the present study had elastic bandages placed on the legs, and some even received foot pumping massages.[11] However, there were no cases of pulmonary embolism detected by enhanced computed tomography in the present study. The second possible mechanism is the complication of infection. The FDP level can be increased by infection.[12] Severe trauma itself can complicate infection, in addition to infection through a venous route, drainage tube, or tracheal tube. However, even after excluding the complications of infection, as determined by an increase in the CRP level, the increase in the FDP level from the 5th hospital day remained in the present study. In addition, the white blood cell count on the 4th and the 5th hospital days did not differ to a statistically significant extent (data were not shown). The third possible mechanism is complications associated with DIC/coagulopathy. Both FDP and D-dimer are considered to be nonspecific markers that cannot be utilized independently. It gains strength only when correlations are identified in the presence of DIC/coagulopathy and in combination with other routine tests. However, none of the participants in this study fulfilled the DIC criteria during hospitalization. The fourth mechanism is the dissolution of thrombus or hematoma induced by initial damage. Cade *et al*. reported the effects of experimental hematomas on the serum levels of fibrinogen-related antigen (FRA) using a radioactive technique in rabbits.[13] They showed that the peak of the level of FRA originating from hematoma was from 70 to 130 h after injury. Accordingly, the increase in the FDP level from the 5th hospital day may be due to the resolution of the clot or thrombus at the injured site.

The clinical implications of the time course of FDP demonstrated in the present study are as follows: the FDP level is a biomarker that indicates the possibility of delayed traumatic hemorrhaging, complications of deep-venous thrombosis, fatal pulmonary embolism, cerebral embolism, aortic dissection infection, and/or DIC/coagulopathy.[2] Especially, previous reports have stressed the importance of monitoring the levels of FDP or D-dimer during hospitalization to detect deep-venous thrombosis or pulmonary embolism.[13-18] If the natural time course of the FDP level after trauma can be determined, physicians can easily make a differential diagnosis for the increase in the FDP level between a natural posttraumatic time course and complication with any of the above-mentioned diseases.

One limitation associated with this study was its retrospective nature and small patient population. In addition, the exact mechanism underlying the increase in the FDP level from the 5th hospital day was not determined. As only about half of the analyzed patients underwent screening for thrombotic complications, an elevation of the FDP level on the 5th day might not represent the natural time course but instead may indicate the presence of an asymptomatic pulmonary embolism and/or deep-venous thrombosis. Furthermore, the time course of the FDP level after the 7th hospital day was not investigated. Accordingly, future prospective studies involving a greater number of traumatized patients are needed to determine the natural time course of the FDP or D-dimer levels in the long term, while also clarifying when the FDP levels return to the normal limits among traumatized patients without complications.

Conclusions

Among trauma patients, the average level of FDP significantly diminished day by day from admission to the 4th hospital day; however, from the 5th hospital day, the average level significantly increased. Further studies are needed to determine the time course of FDP or D-dimer levels in the long term and when FDP levels return to normal limits.

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Conflicts of interest

There are no conflicts of interest.

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