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The Etiological and Prognostic Value of Factor VIII in Patients Diagnosed with Myocardial Infarction: A Prospective Controlled Randomized Study

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Abstract

Aim: The purpose of this study was to evaluate the association between factor VIII (FVIII) and myocardial infarction. A comparative study was performed on patients diagnosed with acute myocardial infarction with/ non-ST-elevation myocardial infarction (STEMI/NSTEMI) and patients presenting with non-cardiac chest pain and no evidence of myocardial injury on electrocardiogram and troponin testing.

Materials and Methods: We evaluated 55 patients with acute STEMI or NSTEMI. The control group consisted of individuals between the ages of 18 and 80 who presented to the emergency department with chest pain and had no electrocardiogram and troponin changes after 0, 1, and 3 hours of follow-up. Samples for FVIII levels were collected from patients and control group at minute 0 on admission.

Results: The mean FVIII levels in the patient and control groups exhibited a notable disparity, yet this difference was not statistically significant. In the patient group, FVIII levels were compared between the STEMI and NSTEMI subgroups, and no significant discrepancy was identified (p=0.226). Furthermore, FVIII levels did not demonstrate a statistically significant divergence in patients with a prior diagnosis of coronary artery disease (p=0.79). In our acute coronary syndrome cohort, women exhibited significantly elevated FVIII levels compared to men.

Conclusion: This study revealed no correlation between FVIII levels and acute myocardial infarction. The findings indicated that there is no significant difference between STEMI and NSTEMI for FVIII levels in subgroup analysis and no significant risk for recurrent coronary events.

Keywords: Acute coronary syndromes, Factor VIII, non-ST elevated myocardial infarction

Introduction

Myocardial infarction (MI) is defined as ischemia-induced myocardial cell death and is one of the leading causes of mortality and morbidity worldwide (1,2). Although the risk of MI increases with age (3), a significant increase has been observed in young patients in recent years (4). The increase in the number of patients presenting with coronary disease and the concurrent reduction in the mean age of this patient group have highlighted the urgency to investigate a broader set of potential causes than previously considered, including factors such as hypertension, obesity, family history, diabetes, hyperlipidemia, and tobacco use (5). Atherosclerotic plaque rupture, coronary dissection, hypercoagulability, drug effects, vasospasm, coronary embolism, and autoimmunity have been identified as potential contributors to the pathogenesis of acute MI (6). However, there is a paucity of research examining factor VIII (FVIII) levels, which are a risk factor for venous thrombosis due to hypercoagulability, in the etiology of coronary thrombosis. FVIII, a crucial protein in the blood coagulation cascade, has been implicated in the development of venous thrombosis. It has been established that elevated FVIII levels are a known risk factor for venous thrombosis (7). However, the role of this factor in arterial thrombosis, such

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as acute MI, remains unclear. The findings of this study may inform the development of novel therapeutic and preventive pharmacological strategies and may be valuable for identifying treatments that can be employed to reduce the burden of arterial thrombosis.

Materials and Methods

Our study was accepted according to the ethical rules with the decision of Atatürk University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (decision no: 13, date: 28.03.2016).

Trial Design

This prospective study was conducted at the Research Hospital, Faculty of Medicine, Atatürk University, Erzurum, Turkey, within the Department of Emergency Medicine. The diagnosis and treatment guidelines for acute coronary syndromes (ACS) published by the American Heart Association were used for all patients with suspected ACS. Furthermore, the dynamic changes between the prehospital electrocardiogram (ECG) obtained by the emergency service team and the ECG obtained in the emergency department (ED) upon arrival were carefully considered. Patients admitted to the ED will be evaluated by interns, emergency physicians in training (assistants), and ED specialists. From patients who met the definition of ST-elevation myocardial infarction (STEMI), an appropriate sample for biochemical parameters and FVIII was obtained, and the patient was transferred directly to the angiography unit as soon as possible. Appropriate samples for FVIII were obtained from patients presenting with cardiac chest pain on admission and were included in the study when a diagnosis of NSTEMI was made.

Participants

Patients who applied to the Atatürk University Emergency Medicine Department over a 3-month period with a chief complaint of chest pain. The study included 64 patients aged 18 years and older (32 patients with STEMI) and 32 patients with non-ST-elevation myocardial infarction (NSTEMI) who were diagnosed with STEMI or NSTEMI in light of clinical evaluation and biochemical assays according to the fourth universal MI definition. Samples were collected to measure FVIII levels in patients after obtaining consent. Patients who had received fibrinolytic for MI at different centers, patients with ECG and/or troponin positivity, sepsis, hypovolemia, heart failure, acute pulmonary embolism, aortic dissection, myocarditis, myocardial contusion, drug toxicity (including kounis syndrome, cardiotoxic agent used), carbon monoxide poisoning, renal failure and cerebrovascular event (ischemia or hemorrhage) were excluded. The control group consisted of 64 healthy individuals aged 18 years and older without cardiovascular disease, diagnosis of thrombophilia, and/or diagnosis of hemophilia A who presented to our ED with chest pain without ECG and troponin changes after 6-8 hours. The patient and control groups were included in the study via simple randomization.

Interventions

To measure FVIII levels, venous blood samples were placed in tubes containing 3.2% sodium citrate with light blue caps. These samples were centrifuged at 4500 rpm for 5 minutes at +4°C to obtain plasma. Plasmas were stored at -80˚C. The frozen plasmas were thawed at the time of analysis and run on the ACL TOP 700 Coagulometer, and the results were evaluated.

Sample Size

A sample size of 128 individuals was planned for the study, with 64 patients in each of the two groups, to achieve an effect size of 0.5, 80% power, and a 5% margin of error (8). However, one sample from the control group and nine samples from the patient group were excluded due to an error in the laboratory measurement process that resulted in excessive hemolysis.

Statistical Analysis

The SPSS 22.0 package, which is compatible with Windows, was used for the statistical analysis of the data. Frequency analysis and percentages were calculated for the demographic characteristics of the groups. The mean and standard deviation were calculated for the numerical data. The chi-square test was used to compare the categorical data. The Student's t-test was used to compare continuous variable data. The Kendall regression test was used to determine the relationship between the laboratory parameters. The significance level was set at $p<0.05$.

Results

A summary of demographic, clinical, and laboratory data is presented in Table 1. A total of 55 patients with ACS were included in the study, of whom 26 had STEMI and 29 had NSTEMI. The study cohort comprised 11 female patients (20%) and 44 male patients (80%). The mean age was 63±14 years (range: 23-91 years). A total of 63 patients were included in the volunteer group. The control group was composed of 28 female patients (45.5%) and 35 male patients (55.5%). The mean age was 42±16 years.

The mean FVIII levels in the patient and control groups were significantly different but not statistically significant. The STEMI and NSTEMI groups were subgrouped within the patient group and FVIII levels were compared, and there was no significant difference ($p=0.226$). FVIII levels were not significantly different in patients with known coronary artery disease ($p=0.79$). In our

ACS group, FVIII levels were significantly higher in women than in men (Table 2). A total of 10% (n=5) of patients exhibited low FVIII levels (i.e., <70% activity), while high FVIII levels (>150% activity) were observed in 14.5% (n=8) of patients. The remaining 42 patients (75.5%) exhibited normal FVIII levels (70-100% activity).

Twenty-three patients (41.8%) were admitted with anterior MI and 25 (45.4%) with inferior MI. The results are presented in Table 3.

Correlations were found between biochemical parameters and survival, with statistically significant results observed for hematocrit (p=0.029), aspartate aminotransaminase (AST) (p=0.006), and albumin (p=0.02) values. A comparison of the remaining parameters is presented in Table 4.

AST (p=0.003) and alanine transaminase (p=0.014) levels were significantly elevated in patients with a known history of coronary artery disease compared with those without such a diagnosis. A correlation was observed between the degree of coronary artery narrowing and the AST, as illustrated in Figure 1.

Table 1. Demographic characteristics and biochemical parameters

Characteristics	STMI Mean (min-max)	NSTEMI Mean (min-max)	Control Mean (min-max)	p value	Reference ranges
Gender (Female%-n)	54.5-6	45.5-5	71.8-28	0.017	-
Age	64.58 (45-91)	61.97 (23-89)	41.81 (19-85)	0.5	18-90
Factor VIII	112 (31-346)	92 (37-238)	91 (28-233)	0.22	70-150
WBC (*10^3 µL)	12.3 (6.5-23)	9.3 (4-19.5)	7.9 (7-19.5)	0.021	4.3-10.3
Lymphocyte (*10^3 µL)	3 (0.8-7)	2 (0.7-6)	2 (4.7-5.1)	0.04	1.3-3.6
Neutrophil (*10^3 µL)	7.8 (0.8-21.6)	5.7 (2.4-16)	4.7 (1.8-16)	0.12	2.1-8.1
HGB (g/dL)	14.5 (12.4-17.4)	14.5 (9-18)	15.5 (10.3-20)	0.1	13.6-17.2
HCT (%)	47 (37-60)	44 (28-53)	45 (33-56)	0.08	39.5-50.3
MCV (fL)	92.5 (81-101)	89 (59-112)	85 (69-91)	0.13	80.7-95.5
RDW	13.5 (12-16)	14 (11-19)	13 (12-19)	0.54	
AST (U/L)	70 (15-311)	103 (13-446)	22 (13-58)	0.25	1-50
ALT (U/L)	43 (13-289)	52 (8-344)	22 (7-62)	0.62	1-60
Albumin (g/dL)	4.02 (3.5-4.6)	3.97 (2.94-4.7)	4.1 (3.3-4.9)	0.67	3.5-0.2
Troponin (ng/mL)	6 (0-58.6)	10.4 (0-67.4)	0 (0-0.2)	0.32	0.01-0.04

STEMI: ST-Elevation Myocardial Infarction, NSTEMI: Non-ST-Elevation Myocardial Infarction, WBC: White blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular Volume, RDW: Red cell distribution width, AST: Aspartate aminotransferase, ALT: Alanine transaminase

Table 2. Factor VIII levels for gender

	Female	Male	p value
Factor VIII (Median ± SD) (min-max)	108±76.5 (28-346)	89±54.2 (29-311)	0.009

SD: Standard deviation

Table 3. Distribution of affected vessels

	LAD	RCA	CX	Normal	Total
Patient (n)	23	18	7	7	55
Patient (%)	41.8	32.7	12.7	12.7	100
Factor VIII (Median ± SD) (min-max)	104±82 (31-315)	123±90 (37-346)	67±45 (46-181)	93±46.5 (28-233)	124±78 (28-346)

LAD: Left anterior descending artery, RCA: Right coronary artery, CX: Circumflex artery

Tablo 4. Effect of biochemical parameters on survival

Characteristics	Discharged (n=50)	Exitus (n=5)	Control (n=63)	p value	Total (n=118)
Age	63±15	68±10	42±16	0.45	52±18
Factor VIII	118.8 ± 74.537	177.2±98.7	101.8±47.3	0.11	112.2±64
HTC	42.3±6.3	48.3±1.97	44.98±4.6	0.029	45.2±5.3
RDW	13.8±1.5	13.3±0.6	13.2±1.4	0.43	13.5±1.4
AST	76±98	208±115	22±7	0.006	53±80
ALT	38±51	147±111	22±13	0.09	35±48
ALbumin	4.04±0.4	3.6±0.4	4.1±0.4	0.02	4.1±0.4
Troponin	8.76±17	4.43±8.1	0,00532± 0.026	0.58	3.9±11.9
Obstruction (%)	85.6±31.6	98±4.5	-	0.39	86.8±30.3

WBC: White blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, RDW: Red cell distribution width, AST: Aspartate aminotransferase, ALT: Alanine transaminase

	LYMP	WBC	FVIII	NEU	HGB	HTC	RDW	PDW	PLT	Ca	AST	ALT	ALB	hsTN	PTT	OBS%
Lymphocyte	1	0.18	-0.14	-0.76	0.17	0.22	-0.19	-0.09	0.22	0.21	-0.11	0.02	-0.1	-0.15	0.05	0.19
WBC	0.18	1	-0	0.74	0.17	0.09	0.065	0.06	0.32	0.25	0.2	0.2	0.21	0.15	0.003	0.22
Factor VIII	-0.01	-0.003	1	-0.01	-0.27	-0.26	-0.09	-0.13	-0.04	-0.1	0.02	0.03	-0.2	-0.13	-0.15	0.18
Neutrophile	-0.08	0.73	-0.01	1	0.13	0.05	0.12	0.1	0.21	0.22	0.25	0.19	0.24	0.23	0.01	0.16
HGB	0.17	0.17	-0.27	0.13	1	0.43	-0.11	0.29	-0.02	0.09	0.22	0.15	0.15	0.05	0.11	-0.05
HTC	0.22	0.09	-0.26	0.05	0.43	1	-0.18	0.1	-0.03	0.3	0.07	0.11	0.17	-0.05	0.19	-0.06
RDW	-0.2	0.07	-0.09	0.12	-0.11	-0.18	1	0.21	-0.08	-0.1	0.14	0.04	-0.1	0.2	-0.03	0.09
PDW	-0.09	0.06	-0.13	0.1	0.28	0.1	0.21	1	-0.32	90.2	0.16	0.01	-0	0.18	0.07	0.03
PLT	0.22	0.32	-0.04	0.21	-0.02	-0.03	-0.08	-0.32	1	0.3	-0.1	-0	0.29	-0.03	-0.01	0.13
Ca	0.21	0.25	-0.08	0.22	0.09	0.3	-0.07	-0.19	0.29	1	0.06	0.07	0.39	0.03	0.17	0.1
AST	-011	0.2	0.02	0.25	0.22	0.07	0.14	0.16	-0.1	0.06	1	0.53	0.17	0.46	-0.02	0.16
ALT	0.02	0.2	0.03	0.19	0.15	0.11	0.04	0.007	-0.03	0.07	0.54	1	0.11	0.25	-0.05	0.02
Albumin	-0.05	0.21	-0.17	0.24	0.15	0.17	-0.05	-0.05	0.29	0.39	0.17	0.11	1	0.14	0.09	0.04
Troponin	-0.15	0.15	-0.13	0.23	0.05	-0.05	0.2	0.18	-0.03	0.03	0.46	0.25	0.14	1	0.12	-0.007
PTT	0.05	0	-0.15	0.009	0.11	0.19	-0.03	0.07	-0.01	0.17	-0.02	-0.1	0.09	0.12	1	0
OBS%	0.19	0.22	0.18	0.15	-0.05	-0.06	0.09	0.03	0.13	0.1	0.16	0.02	0.04	-0.01	0	1

LYMP: Lymphocyte, WBC: White blood cell, FVIII: Factor VIII, NEU: Neutrophil, HGB: Hemoglobin, HCT: Hematocrit, RDW: Red cell distribution width, PLT: Platelet, Ca: Calcium AST: Aspartate aminotransferase, ALT: Alanine transaminase, ALB: Albumin, HsTN: High-sensitivity Troponin, PTT: Partial thromboplastin time, OBS: Obstruction

Figure 1. The Kendall's correlation between variables

Discussion

The results revealed no significant difference in FVIII levels between the ACS and control groups. Furthermore, no correlation was observed between FVIII levels and patient prognosis. The subgroup analysis demonstrated no significant difference between STEMI and NSTEMI for FVIII levels, and no significant difference was observed in recurrent coronary events.

Prior research has demonstrated that FVIII levels are elevated in women relative to men in the context of venous thromboembolism, with the underlying mechanism attributed to oral contraceptive (OCS) usage (9). Similarly, in the ACS group, FVIII levels were significantly higher in women than in men, although there was no history of OCS use in the study group. Given the age range of the patients in the control group, it was hypothesized that they might have the potential to use OCS. In a study by von Kanel et al. (10) investigating the increase in FVIII levels associated with physiological stress, FVIII levels were found to be lower in patients treated with acetylsalicylic acid (ASA) + propranolol compared with those receiving ASA alone, propranolol alone or placebo. The majority of patients in the study group were transported to the ED by ambulance following the administration of the recommended dose of ASA (325 mg) in the prehospital setting, irrespective of whether the patients were chronic ASA users or not. In light of the aforementioned evidence, the FVIII levels of our patients may have been influenced.

In a study published in 1990, Rosendaal et al. (11) observed that low FVIII levels were associated with a reduced risk of developing ischemic heart disease. Patients with FVIII levels >200 IU/dL had a threefold increased risk of recurrent thrombosis, according to Timp et al (12). However, the results of the study conducted by Šrámek et al. (13) indicated that high FVIII levels were associated with venous rather than arterial thrombosis. Zakai et al. (14) showed that high FVIII levels were associated with both increased stroke and coronary artery disease. In this study, participants were contacted via telephone, basic demographic and risk factor data were collected, and COX modeling was performed. A recent literature review indicated that abnormalities in the coagulation cascade that predispose to thrombosis increase the risk of stroke in young patients more than MI (15). The pathology in our study group was coronary artery occlusion, and there was no significant difference in FVIII levels between the study and control groups.

Study Limitations

It should be noted that the present study is subject to certain limitations. The most significant limitations of this study are the relatively small number of patients and the lack of multi-centered recruitment. A larger patient population and a more diverse geographical range would yield more effective results. Many medications affect FVIII levels. The absence of data on the medications used by the patients represents a significant limitation of our study. FVIII levels were measured only from the initial blood samples collected upon patient arrival. Further measurements are required to demonstrate potential changes in levels. The inability to perform consecutive measurements represents another limitation of our study.

Conclusion

This study revealed no correlation between FVIII levels and acute MI. The findings indicated no significant difference between STEMI and NSTEMI for FVIII levels in the subgroup analysis and no significant risk of recurrent coronary events. A larger sample size would allow for the design of studies that could demonstrate a statistically significant difference in the effect of FVIII on arterial thrombosis.

Ethics

Ethics Committee Approval: Our study was accepted according to the ethical rules with the decision of Atatürk University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (decision no: 13, date: 28.03.2016).

Informed Consent: Samples were collected to measure FVIII levels in patients after obtaining consent.

Footnotes

Authorship Contribution

Surgical and Medical Practices: M.G., Concept: M.G., Design: M.G., Data Collection or Processing: M.G., S.D., T.S.M., Analysis or Interpretation: M.G., A.T., Literature Search: M.G., Writing: M.G., A.T.

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