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Original Article

Opium Addiction and Coagulation Factors in ST-Segment Elevation Myocardial Infarction (STEMI) Patients: Implications for Thrombosis and Cardiovascular Outcomes

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Abstract

Background: Myocardial infarction (MI) is one of the most common causes of death globally. Since a comprehensive study on the relationship between coagulation factors in AMI patients and opium consumption has not been done, in this study the effect of opium consumption on the number of coagulation factors I, II, VII, IX, and XI in patients with myocardial infarction and ST-elevated (STEMI) was investigated. Furthermore, our results shed light on the relationship between opium and coagulation factors with thrombosis grades.

Methods: In this case-control study, 80 STEMI patients referred to Razi Birjand Hospital, Iran, between years 2021 to 2022 were divided into two groups of opium addicts and non-addicts based on opium consumption and non-addict use, and the levels of the mentioned coagulation factors in their plasma were measured and compared with the corresponding values in 80 healthy people. Collected data was analyzed using SPSS software. The significance level of all tests was 5%.

Results: The number of coagulation factors I, II, VII, and IX, unlike factor XI, in the opium addict group was significantly higher than the other two groups. While there was no statistically significant relationship between these coagulation factors with different degrees of thrombosis, most of the studied population were classified as Grade 5. Results also suggest no significant correlation between biochemical parameters and opium consumption.

Conclusion: Opium consumption can cause thrombosis by increasing the level of some coagulation factors. The findings from this study could have implications for clinical practice and public health interventions related to opium addiction and its impact on cardiovascular outcomes.

Keywords: Opium; Coagulation factor; STEMI; Myocardial infarction

Introduction

Myocardial infarction (MI) is one of the major manifestations of arterial thrombosis and leading causes of death worldwide (1-3). Increased coagulability is a well-known cause of MI, caused by

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an increase in the level of coagulation factors or a decrease in fibrinolytic activity (4). This disorder includes a wide range of inherited and acquired disorders in which the coagulation system is out of balance which makes people more prone to thrombosis (5).

Drug use is currently considered as one of the major concerns of many societies due to its increasing usage trend. This issue is even more catastrophic in Iran, as regarding its proximity to Afghanistan, the major opium producer in the world, the greatest amount of opium has been seized in Iran (6). The number of people suffering from drug addiction in Iran has more than doubled in the last six years, with about 2.8 million people regularly consuming drugs in the country (7, 8).

Opium is the country's most popular narcotic, making up 67% of consumption, followed by marijuana and its derivatives, which account for 12% of drug consumption in Iran (9) and despite the fact that alcohol and narcotics are illegal in Iran, drug addiction is a significant health, medical, and social problem in the country (10).

The situation can become even more complicated because many people and some physicians believe that use of drugs and especially opium can have beneficial effects in improving cardiovascular disorders. Such assumption can persuade people, particularly ordinary ones, towards opium use. (8, 11-13). This issue, however, is in spite of many studies have shown that opium use is a risk factor for cardiovascular diseases (14-17).

However, the relationship between increased coagulability in acute myocardial infarction (AMI) patients and opium consumption has not yet been fully investigated and there is no accurate and complete information on the role of opium in the occurrence of MI (15, 18, 19). For this reason, evaluation of how drug-addiction can impact concentrations of coagulation factors seems to be an interesting question that forms the basis of our research. Our results can improve public awareness about detrimental effects of opium addiction on cardiovascular system and public health.

We aimed to examine the effects of opium consumption on the levels of biochemical parameters, coagulation factors I, II, VII, IX, and XI, and thrombosis grades in patients with ST-elevated myocardial infarction (STEMI) referred to Razi Hospital in Birjand, South Khorasan Province, Iran.

Materials and Methods

Data collection

In this investigation, patients with ST-elevated myocardial infarction (STEMI) referred to Razi Birjand Hospital, Birjand, Iran were categorized into two groups: opium addicts and non-addicts. The study involved measuring the levels of plasma coagulation factors for each individual in both groups as well as healthy individuals. Additionally, the thrombosis grades of the patients were assessed.

The thrombolysis in myocardial infarction (TIMI) thrombus grading scale was utilized to classify thrombosis. According to this system: I. Grade 0: No cine-angiographic characteristics indicating the presence of a thrombus. II. Grade 1: Possible presence of a thrombus. Angiography reveals characteristics such as reduced contrast density, haziness, irregular lesion contour, or a smooth convex meniscus at the site of complete occlusion, which suggest but do not definitively diagnose a thrombus. III. Grade 2: Small-sized thrombus present. It is a definite thrombus with dimensions that are equal to or less than half the vessel diameter. IV. Grade 3: Moderate-sized thrombus present. It is a definite thrombus with the greatest linear dimension greater than half but less than two vessel diameters. V. Grade 4: Large-sized thrombus present. Similar to grade 3, but with the largest dimension equal to or greater than two vessel diameters. VI. Grade 5: Total occlusion.

Patients were interviewed by a single experienced observer blinded to the study. The DSM- IV-TR criteria for opium dependence were used to define addiction (35). All participants were asked to disclose, whether they have ever used any type of

drugs and they were assured that their information will be analyzed anonymously and used only for research purposes. Almost all Iranian people truth on medical doctors to disclose their confidential health-related information.

Inclusion criteria for patient groups were: STEMI diagnosis based on the clinical symptoms, electrocardiogram (ECG) by expert cardiologists. Willingness to sign the written informed consent and participation in the study. Moreover, those who had continuous use of opium for more than a year were identified as opium addicts. For the control group, cases were selected from healthy donors and were matched by sex and age (±5) to those in case groups.

The exclusion criteria were as follows: patients who refused to sign the written informed; those with hemophilia or other bleeding disorders; patients with other thrombotic events such as DVT; individuals who received anticoagulant drugs (such as oral warfarin and rivaroxaban) and receiving enoxaparin or heparin within previous 8 h; those ceased using opium more than a year and patients with metabolic syndrome or cancers.

Sampling Method

The study comprised of 80 addicts and non-addict individuals (40 in each group) who undergone AMI and 80 healthy donors. Patients referred to Razi Hospital, Birjand, Iran between years 2021 to 2022. Blood samples were collected from patients who satisfied the inclusion criteria. The sample was poured into tubes with and without anticoagulant for coagulation and biochemical analysis, respectively. The samples were subsequently stored at -80 ºC until the tests were conducted. Coagulation factors determination was performed by Stago coagulation analyzer, hemoglobin was measured by Sysmex XS-500i, and biochemical analysis was done by Prestig. All Experiments were performed in triplicate.

Statistical analyses

Statistical analysis was performed using SPSS software (ver. 16, Chicago, IL, USA). The Kolmogorov-Smirnov test and histograms were used to evaluate normality. Numerical variables are presented as mean ± SD if they had a normal distribution and as medians [25 percentile, 75 percentiles] if they did not. For non-parametric values in different groups Kruskal-Wallis and Mann-Whitney tests were performed. *P*-values of less than 0.05 were considered as the significant level.

Ethical Considerations

Patients participated in this study completed consent form, all data was collected confidentially and the names of the patients were not mentioned.

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Results

The primary objective of the current study was to examine the impact of opium on the levels of coagulation factors I, II, VII, IX, and XI. Three distinct groups of participants were included: the control group (n=80), the opium group with STEMI (n=40), and the non-opium group with STEMI (n=40). The levels of coagulation factors I, II, VII, and IX were significantly lower in the control group compared to the other two groups. Furthermore, the non-opium group exhibited lower levels of these factors when compared to the opium group. However, no notable difference was observed in the levels of coagulation factor XI between the control group and the other groups (Table 1).

Table 1: Comparison of average coagulation factors in the studied groups. Statistical analysis shows an increase in the level of factors I, II, VII and IX in both opium and non-opium groups compared with healthy controls. factor XI has undergone no changes in both opium and non-opium groups

Variables	Opium Group (Mean ± SD) (n=40)	Non-opium group (Mean ± SD) (n=40)	Healthy subjects (n=80)	*P*-value (Healthy vs Opium)	*P*-value (Healthy vs non-opium)	*P*-value (Opium vs non-opium)
Factor I	330.5±64.6	289.7±69.5	248.1±63.5	<0.001	0.003	0.014
Factor II	142.4±15.8	125.4±16.8	108.9±14.4	<0.001	<0.001	<0.001
Factor VII	140.8±10.1	123.4±12.5	98.2±21.3	<0.001	<0.001	<0.001
Factor IX	146±14.8	131.3±18.2	106.4±20.1	<0.001	<0.001	<0.001
Factor XI	118.1±23.5	117.4±20.9	113.0±21.4	0.258	0.270	0.773

According to the data presented in Table 2, which compares the average concentrations of coagulation factors with different thrombus grades in the studied population, there is no significant statistical correlation between thrombus grades and the levels of coagulation factors I, II, VII, IX, and XI.

Table 2: Comparison of coagulation factors average concentration with thrombus grades in the studied population using the Kruskal-Wallis statistical test. Statistical analysis reveals that there is no significant relationship among thrombus grades and the levels of coagulation factors I, II, VII, IX, and XI

Grade thrombosis	Factor I (Mean ± SD)	Factor II (Mean ± SD)	Factor VII (Mean ± SD)	Factor IX (Mean ± SD)	Factor XI (Mean ± SD)
G0	328.1±69.0	136.0±10.5	131.7±9.6	144.2±22.6	119±22.5
G1	315.1±62.3	139.3±14	141.5±12.6	134.3±14.5	110.5±27.7
G2	289.9±56.7	129.5±12.9	126.5±16.0	136.8±17.6	120.2±17.7
G3	278.2±96.4	123.4±18.8	122.8±16.3	135.2±20.1	97.4±29.2
G4	301.9±70.5	132.7±23.2	127.9±15.5	135.4±20.9	120.0±15.2
G5	312.1±73.8	134.7±20.8	133.2±12.6	138.5±17.4	120.3±23.6
P-value	0.652	0.761	0.214	0.951	0.591

In the present study the frequency distribution of thrombosis grades in patients who underwent angiography was also evaluated. The data analysis revealed that the majority of the studied patients (40%) exhibited grade 5 thrombosis. The results for grade 0, grade 1, grade 2, grade 3, and grade 4 were 10%, 9%, 15%, 7%, and 19%, respectively. According to the Table 3, in terms of biochemical parameters and hemoglobin, no significant differences between groups was observed.

Table 3: Comparison of biochemical variables between opium and non-opium groups. There was no significant correlation between biochemical parameters and opium consumption in patients with myocardial infraction history

Variables	Opium Group (Mean ± SD) (n=32)	Non-opium group (Mean ± SD) (n=38)	*P*-value (Opium vs non-opium)
Triglyceride[1]	116.2±84.0	106.4±68.1	0.6
Cholesterol[2]	149.6±31.0	150.5±35.0	0.9
HDL[1]	38.6±6.4	42.4±9.6	0.2
LDL[2]	97.0±29.8	91.7±27.8	0.5
FBS[1]	126.0±25.9	133.4±43.7	0.9
Creatinine[1]	1.15±0.3	1.1±0.4	0.7
Hemoglobin[2]	14.95±1.9	14.5±1.2	0.4

HDL: High Density lipoprotein; LDL: Low Density lipoprotein; FBS: Fasting Blood Sugar
1. Mann-Whitney U test; 2. *t*-test

Discussion

The relationship between increased coagulability in AMI patients and opium consumption, so far, has been the subject of limited research. For this reason, there is no accurate and complete information on the role of opium in the occurrence of AMI. In addition, the association between opium and cardiovascular disease has been a matter of debate, with conflicting results from various studies (15, 18, 19). Therefore, in this novel study, the effect of opium consumption on the level of coagulation factors I, II, VII, IX, and XI in patients with STEMI was investigated.

Our results show that healthy individuals have significantly lower levels of coagulation factor I compare with both STEMI groups either opium addicted or not. This fact can justify patients' increased susceptibility to thrombosis. STEMI addicted group also showed higher amount of coagulation factor I compare with STEMI patients who are not addicted. Similarly, Masoumi et al 's study showed a higher amount of factors I and VII in opium-addicted men (35). In This study, higher incidence of acute heart attack in drugs users justified by elevated amounts of factors I and VII confirmed by our results (20).

Prothrombin (factor II) is produced in liver and resulting thrombin is an indispensable part of the coagulation process. Several studies implied on the direct association between thrombin levels and increased risk of ischemia and coronary artery disease (CAD) (21, 22). Table 1 demonstrates a direct relation between opium consumption and factor II levels. This relationship, however, was not confirmed by an in-vivo study that investigate the effects of opium on some inflammatory and coagulation factors in golden hamsters. In this study, no meaningful difference in fibrinogen and factor II levels between opium-consuming groups and control was observed (23). This discrepancy may be originated from the variations among animal models or differences in administration routes. Therefore, to address this confliction, more investigations on various animal models with different administration routes should be conducted.

Factor VII is a vitamin K-dependent coagulation factor made in the liver. It causes acute coronary events by triggering extrinsic pathway of the coagulation cascade (24-26). Coagulation Factor IX (FIX, Christmas factor) is another blood clotting factor and a serine protease zymogen. Studies showed that reduced levels of factor VII are known as a protective element against MI (26, 27).

This statement can also be confirmed by our study as both STEMI patients have elevated lev-

els of Factor VII and IX compared with healthy control group. Additionally, our data suggests that both factor VII and factor IX levels can significantly be increased followed by opium addiction.

Additionally, increased factor VII and IX are associated with coronary events and myocardial infraction in healthy individuals (28).

Various coagulation factors were investigated in opium-addicted and non-addicted men. Factors I and VII levels were significantly higher in addicted group compared with healthy control. This finding is in consistent with the results of our research. They also found correlation between these changes with the addiction duration and concluded that addicted individuals are more prone to develop atherosclerotic cardiovascular diseases (29).

Opium addiction can cause atherosclerosis by increasing coagulation factors plasma levels. In addition, addiction may lead people toward depression and make them more isolated form the society and there is also a reduction in their physical activity which in the long term can make people more sustainable to thrombotic complications such as stroke (17, 30, 31).

Factor XI is another liver-produced coagulation factor that although its direct relationship with increased incidence rate of DVT has been fully investigated (32) , there are conflicting results regarding this factor relationship with ACS and/or stroke. Although some studies have shown an increased risk of MI in patients with factor XI elevated plasma levels (33, 34) its deficiency fails to induce any protection against MI (35, 36).

Based on Table 1, we could not find any relation between factor XI levels and CAD neither in healthy individuals nor STEMI groups. Our data can also be confirmed by another study conducted on the North Indian population as it suggested that there is no significant association between higher levels of coagulation factors FIX and FXI and an increased risk of Venous thromboembolism (VTE)(37).

The present study provided valuable insights into the distribution frequency of thrombosis degrees in patients with STEMI who undergoing angiography. Our findings showed that grade 5 thrombosis is the most common thrombosis severity level observed in STEMI patients. Previous studies have reported different distributions of thrombosis grades depending on various medical conditions and studied populations. For instance, in one, patients with STEMI underwent manual thrombus aspiration (MTA) and 98% of these patients had a significant thrombus load and TIMI thrombus burden grade > 4 (38).

While prothrombin levels showed no significant association, higher levels of coagulation factors specifically FVIII, FIX and FXI, were positively correlated with venous thrombosis (VT) in elderly. Primary analysis, however, indicates no distinct linear relationship between the increased amount of coagulation factors and the risk of VT(39) which is in coordination with our results as we found no significant relationship between thrombosis degree and coagulation factors levels. However, further research is required to determine whether these results are representative of the larger population and whether other risk factors or medical comorbidities are associated with these thrombosis grades or not.

In explaining the exact mechanism of the opium effect, it is said that opioid receptors in the ventricles and arteries may play a key role in the occurrence of various arrhythmias such as tachycardia and bradycardia. In low doses, this phenomenon in probably occurs through the activation of kappa receptors while in high doses of opium, through a direct reaction with the membrane of heart cells (17, 40).

No significant variation detected in the average serum total cholesterol levels between drug abusers and non-drug abusers. Nevertheless, the average low-density lipoprotein cholesterol and triglyceride levels in drug addicts were significantly greater compared to non-drug users. Notably, the prevalence of diabetes and glucose levels were markedly lower among opium addicts (41). While these results are in contrast with ours as we found no correlation between these biochemical

parameters with opium addiction, our findings can be confirmed by several studies (30, 42).
There were some limitations in the present study. Lack of the opium-addiction confirmation test was a main limitation but since written contest was taken from participants and their first-degree relative, this issue would not interfere results significantly. In addition, the administration of opium can occur through various methods which may affect their concentration in the blood. Therefore, considering how these different routes may influence variations in coagulation factors is considered to apply in our future studies.
Taken together, our findings suggest that unlike the commonly held notion, opium consumption not only is not associated with beneficial effects on cardiovascular health or biochemical parameters but also it can rise the chance of coagulopathies by increasing coagulation factors concentrations.
Authors also recommend more in-depth studies with a larger sample size to further investigate the potential risk of opium addition and its underlying mechanisms in thrombus formation. It is reasonable that addicted individuals should be regularly monitored for any changes in their coagulation profile and appropriate interventions and management should be undertaken, especially for those with risk factors or history of thrombosis.

Conclusion

Opium consumption increases the risk of STEMI. However, further research is required to investigate long-term effects of opium use on these parameters and to clearly identify possible risk factors or comorbidities that can impose thrombotic disorders.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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