ORIGINAL REPORT

The Effect of Opium Addiction on Arrhythmia Following Acute Myocardial Infarction

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Abstract- The effect of opium addiction on the appearance of different types of arrhythmias after acute myocardial infarction (AMI) has been assessed in few studies. This study is aimed to determine the effect of opium on post-MI arrhythmia and also to address the differences in the appearance of different types of arrhythmias after AMI between opium addicted and non-addicted patients. In this comparative study, participants were classified into two groups with opium addiction (n=94) and without opium addiction (n=106). Post-MI arrhythmias were determined among each group. Study populations were included all patients with first AMI admitted within 6 hours of the onset of chest pain to coronary care units (CCU) of two teaching hospitals affiliated to Kerman University of Medical Sciences (KUMS) in the city of Kerman, Iran. Opium addicted subjects had significantly more frequency of arrhythmia than non-opium addicted subjects (80.9% vs. 22.6%, respectively; $P<0.001$). Opium addiction was a strong predictor for the occurrence of post-MI arrhythmias in two models of crude analysis (crude OR=14.4, $P<0.001$) and after adjusting for potential confounder factors (adjusted OR = 21.9, $P<0.001$). The prevalence of sinus tachycardia, sinus bradycardia and atrial fibrillation in opium addicts were significantly higher than non opium addicts ($P<0.05$). The results of our study showed that opium addiction is a potential and strong risk for occurring post-MI arrhythmias.

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Keywords: Addiction; Arrhythmia; Myocardial infarction; Opium

Introduction

Despite opium use is considered to have a declining trend in most societies, recent data have shown notable attendance to opium usage in some developing countries such as Iran (1-3). The incidence of opium addiction is especially higher in some patients populations so that the prevalence of opium addiction is about 2-2.8 percent among Iranian general population; whereas it was estimated about 9.9-19 percent in the group with acute myocardial infarction (4,5). The most important reason for this high prevalence is the misconception in our population that opiates can prevent and control risk factors for coronary artery disease (CAD) such as hypertension and diabetes mellitus and also has an ameliorating effect in the process of these factors (4). This belief about protective cardiovascular effects of opium has been extended even among some physicians that believe an alternative role for opium in management of some cardiovascular risk factors such as diabetes (6,7). However, this belief has not been supported by some recent basic and clinical investigations. In some of them, serum levels of biochemical risk factors for CAD such as lipoprotein (a) and C-reactive protein were significantly higher in opium addicted patients and these are major determinants of premature atherosclerosis (8). Furthermore, some basic trials have confirmed that opioid peptides involve in ischemic preconditioning via K_{ATP} channels in cardiac mitochondria that play a pivotal role in a number of pathological conditions in cardiovascular system (9,10). However, some other studies provided some evidences in protective role of opium use. Marmor *et al*. indicated that long-term exposure to opiates was associated with decreased severity of CAD, and hence with decreased incidence of fatal myocardial infarctions (11).

Also, Najafi *et al* revealed that the different domains of quality of life in opium-addicted and non-addicted

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patients with CAD were not statistically different (12). There is controversy among clinicians about the effects of opium addiction on the cardiovascular system. In addition, these effects on outcome of different subgroups of acute myocardial infarction (AMI) have been unclear. In an experimental study, Najafipour *et al.* showed that opium smoking especially in hypercholesterolemic condition was a predisposing factor for ventricular tachycardia (VT) and fibrillation (VF) in rabbits subjected to cardiac ischemia (13).

There are controversy results regarding the effect of opium use on the appearance of post-MI arrhythmias. Some authors have shown that the opioid receptors have crucial role that the μ-type receptors has stimulatory and κ-type receptors has inhibitory effects on cardiac rates and systolic hypertension (14,15). It was also found that the influence of opium is mediated by the autonomic system that can lead to the increase of systolic blood pressure in hypertensive patients (16). However, data published regarding the effect of opium addiction on the occurrence of arrhythmias following AMI is rare. Therefore, the present study is aimed to address the differences in the appearance of different types of arrhythmias following AMI between opium addicted and non-addicted patients.

Materials and Methods

Participants and setting

The study population consisted of 200 patients with first acute myocardial infarction admitted within 6 hours of the onset of chest pain to coronary care units (CCU) of the two of the biggest teaching university hospitals in the city of Kerman, Iran between December 2010 and May 2011. Inclusion criteria were: 1) typical chest pain lasting ≥30 min; 2) ST-segment elevation ≥0.2 mV in ≥2 contiguous precordial leads (for the diagnosis of anterior wall MI) or ≥0.1 mV in leads II, III, and aVF (for the diagnosis of inferior wall MI) on the admission ECG; 3) no previous myocardial infarction; 5) no other heart or lung disease. After describing the conditions of the study, a written informed consent was obtained from each participant. This study was approved by ethical committee of Kerman University of Medical Sciences.

Participants were classified into two groups of opium addicted (n=96) and non-addicts (n=106) and post MI-arrhythmia and types of arrhythmia were determined in each group. All participants received streptokinase immediately after diagnosis. Opium addiction was defined on the basis of the DSM-IV criteria for substance dependence (regular consumption of inhalatory opium more than three times per week and/or oral opium daily) (17). All patients consumed opium regularly before and after enrollment into the study, it means all opium users could use opium regularly when they were hospitalized, and withdrawal syndrome was not appeared in none of patients.

Definition of post-MI arrhythmia

Study subjects with first acute myocardial infarction hospitalized within 6 hours of the onset of chest pain to coronary care units (CCU). Each patient underwent 24-48 hour Holter monitoring (continuous ambulatory electrocardiographic monitor) to record continuous ECG signals. At the end of the measurement period, a blinded cardiologist read the ECG printouts and reports of post-MI arrhythmias. Types of arrhythmias including VT, premature ventricular contractions (PVC), sinus tachycardia, sinus bradycardia, atrial fibrillation and other [consisted of complete heart block (CHB), premature arterial contractions (PAC), paroxysmal supraventricular tachycardia (PSVT)] were recorded.

Data collection

Demographic characteristics and clinical criteria of these patients were extracted from hospital record files as well as face to face interviewing if required. A check list about medical history and early complications after MI were completed that included: general characteristics, CAD risk factors: cigarette smoking history (current smoking vs. ex-smokers and non-smokers) (18), hypercholesterolemia (total cholesterol ≥5.0 mmol/l, HDL-cholesterol ≥1.0 mmol/l in men, or ≥1.1 mmol/l in women, and triglycerides ≥2.0 mmol/l) (19), family history of CAD (in first-degree relatives before the age of 55 in men and 65 years in women) (20), hypertension (systolic blood pressure ≥140 mmHg and/or diastolic ≥90 mmHg and/or on antihypertensive treatment) (21) diabetes mellitus (symptoms of diabetes plus at least one of the following: plasma glucose concentration ≥11.1 mmol/l, fasting plasma glucose ≥7.0mmol/l, and 2-hpp ≥11.1 mmol/l) (22). All patients underwent two-dimensional echocardiography and those with the left ventricular ejection fraction < 40% were excluded from the study.

Statistical analysis

Results were reported as mean ± standard deviation (SD) for the quantitative variables and relative and absolute frequencies for the categorical variables. The groups were compared using the Student's t-test for the continuous variables and the Chi-square test (or Fisher's

exact test if required) for the categorical variables. Univariate and multivariate logistic regression analysis were used to investigate the effect of opium addiction on post-MI arrhythmia as a predictor factor. Crude and adjusted odds ratios (ORs) along with their 95% confidence intervals (CI95%) were reported. All the statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). *P*-values less than 0.05 were considered statistically significant.

Results

Regarding differences in baseline characteristics and clinical indices (Table 1), no differences was observed in sex ratio and mean age between the patients with opium addiction and those without opium addiction. But, overall frequency of hypertension, cerebrovascular disease, hyperlipidemia and mean left ventricular ejection fraction were significantly more prevalent in non-opium addiction group than those in group of opium addiction ($P<0.05$), but cigarette smoking in opium addiction was more prevalent ($P<0.05$). Two study groups had similar frequency of diabetes mellitus, previous CCU admission and CK-MB rising ($P>0.05$). No significant difference was also observed between the two study groups in type of myocardial infarction so that the anterior MI was occurred in 64.9% of the opium addict group and 55.7% of patients without opium addiction ($P=0.18$). Among drug history, just metformin was frequently used in opium addiction group than non-opium addiction (26.6 vs. 3.8%, $P<0.001$).

The prevalence of post-MI arrhythmia in the group of opium addicts was more prevalent than those were non-opium addicts (80.9 vs. 22.6, $P<0.001$). The most common type of post-MI arrhythmia in opium addicts were PVC and VT. The prevalence of these arrhythmias in opium addicted and non-addicted patients were 21.3%, 16% and 0%, 8.5%, respectively. Results in Table 2 show that PVC, sinus bradycardia, atrial fibrillation in opium addicts were higher than non-opium addicts that this difference was statistically significant ($P<0.05$). Other types of arrhythmias including VT and sinus tachycardia were not statistically significant between two groups (Table 2). Post-MI arrhythmia was significantly more in opium addicted men than addicted women (100% vs. 76.3%, $P=0.002$). Duration of opium use was also longer in patients with arrhythmia compared with patients without arrhythmia (11.8 ± 9.4 vs. 5.5 ± 3.2 years, $P= 0.019$).

Table 1. Baseline characteristics and clinical data of the patients in two groups.

Variables	**Opium addicts (n=96)**	**Non-opium addicts (n=106)**	***P*-value**
Male gender	76 (80.9)*	86 (81.1)	0.96
Age, year	60.3±11.6**	58.8±11.9	0.34
Diabetes mellitus	29 (30.9)	22 (20.8)	0.102
Hypertension	21 (22.3)	41 (38.7)	0.013
Cigarette smoking	15 (16)	7 (6.6)	0.035
Cerebrovascular disease	0 (0)	6 (5.7)	0.031
Hyperlipidemia	3 (3.2)	14 (13.3)	0.011
Previous CCU admission	36 (38.3)	31 (29.2)	0.17
LV ejection fraction	46.2±5.1	47.8±6.2	0.041
CK-MB rising	82 (87.2)	84 (79.2)	0.13
Type of MI			
Anterior wall	61 (64.9)	59 (55.7)	0.18
Inferior wall	33 (35.1)	47 (44.3)	
Drug history:			
Aspirin	38 (40.4)	42 (39.6)	0.99
Atorvastatin	31 (33)	42 (39.6)	0.33
Nitrocantin	25 (26.6)	28 (26.4)	0.97
Losartan	27 (28.7)	25 (23.6)	0.40
Captopril	8 (8.5)	10 (9.4)	0.82
Metoral	6 (6.4)	12 (11.3)	0.22
Metformine	25 (26.6)	4 (3.8)	<0.001
Glybenclamide	10 (10.6)	8 (7.5)	0.44

* Values are represented as n (%), ** mean ± standard deviation

Table 2. Most common types of post-MI arrhythmia in two groups of opium addicted and non-opium addicted.

Arrhythmias	Opium users (n=94)	No opium users (n=106)	*P*-value
All arrhythmia	76 (80.9)	24 (22.6)	<0.001
Ventricular tachycardia	15 (16)*	9 (8.5)	0.105
PVC	20 (21.3)	0 (0)	< 0.001
Sinus tachycardia	9 (9.6)	9 (8.5)	0.78
Sinus bradycardia	12 (12.8)	3 (2.8)	0.008
Atrial fibrillation	9 (9.6)	3 (2.8)	0.045
Other (CHB, PAC, PSVT)	11 (11.7)	0 (0)	<0.001

* Values are presented as n (%)

Table 3. Multivariable logistic regression analysis for determining role of opium use on the occurance of arrhythmia after acute myocardial infarction.

Characteristics	Adjusted Odds Ratio	95% Confidence Intervals	*P*-value
Opium use	21.9	9.58 – 50.01	< 0.001
Hypertension	0.76	0.32 – 1.76	0.527
CVA	1.023	0.988 – 1.060	0.202
Hyperlipidemia	2.97	0.72 – 12.2	0.13
Cigarette smoking	2.64	0.62 – 11.2	0.18
Metformine use	0.55	0.18 – 1.68	0.30
LV ejection fraction	1.017	0.94 – 1.09	0.64

The odds of having any types of post-MI arrhythmias in opium addiction was also higher than those without opium addiction (crude OR=14.4, 95% CI =7.26-28.65, *P*<0.001). after adjusting for confounder factors, multivariate logistic regression model (Table 3) showed that the opium addiction was a strong predictor for the occurrence of arrhythmias after AMI with the presence of cofounder variables (OR=21.9, *P*<0.001). Other variables listed in Table 3 were not significant predictors for post-MI arrhythmia.

Discussion

The present study showed a strong relationship between opium addiction and occurrence of post-MI arrhythmias in the patients who were admitted at the CCU wards within the first hours after AMI. The main finding of the present study was to confirm this association so that the different types of post-MI arrhythmias were considerably more prevalent in addicted patients than non-addicts and the former population are strongly at high risk for these events. This significant relation was also demonstrated in a multivariable logistic model with the presence of potential cofounders. To the best of our knowledge, only two published studies have focused on similar purpose. In a published case report by Gad *et al.* (23) some evidences were obtained regarding the presence of atrial flutter in a neonate with an opium addicted mother. In another observational study by Gorgaslidze *et al.* (24) opium consumption led to the sinus tachycardia in at least two-third of the study subjects.

In the present study, we also showed that opium addiction frequently could result in the occurrence of PVC and sinus bradycardia and thus other arrhythmias especially originated in atrium were rarely occurred. In fact, the main pathophysiology of the appearance of post-MI can be directly related to the abnormalities in conduction system. The types of opioid receptors in the ventricles might have major role in this context. As previously discussed, it seems that the μ_1-type receptors can increased cardiac rate as well as affect cardiac rhythm and therefore can mediate post-MI arrhythmia in the addicted ones (15,16). It has also been showed that opioid peptides can stimulate autonomic nervous system and increase heart rate and systolic blood pressure (14). This might be another primary underlying etiology for occurrence of post-MI tachyarrhythmias. Moreover, some authors have hypothesized that an intravenous dose of some μ -receptor selective opioid peptides can suppress baroreflex sensitivity through a peripheral mechanism. In fact, activation of these receptors present

in the vagus nerves inhibits reflex bradycardia in animal (25).

Other finding of the present study was to no significant difference between opium addicts and non-opium addicts regarding to sinus tachycardia and VT that was similar occurrence in two groups. Most evidences on the effects of opium or opioid-like substances on cardiac rates have been focused on animal studies, some opioid receptors with the different actions have been revealed. Endogenous opioid peptides are associated with the sympathetic and parasympathetic nervous systems, particularly in areas of the brain stem involved in the control of cardiovascular function. It has been suggested that the postganglionic sympathetic nerve fibres innervating the rat heart are endow with presynaptic opioid OP_4 and cannabinoid CB_1 receptors, activation of which inhibits the neurogenic tachycardia (26). It has also been observed that the high affinity μ_1-opioid receptors mediate tachycardic responses and μ_2-receptors mediate bradycardic responses (27). Finally, the inhibitory effects of opium use on sinus tachycardia and VT especially in human subjects need more investigation.

Our study had some limitations. First, our study enrolled a small number of patients. In addition, the route and quantity of opium use should be considered to support these hypotheses. Therefore, further studies considering route and measure, particularly in greater sample sizes are recommended. Another limitation of this study was its design. This research was a cross-sectional comparative study that compared two groups according to their history of opium consumption. Evidences have shown that the retrospective studies have not enough power to prove the relationships between an exposure such as opium use with a disease such as cardiac arrhythmia. Therefore, to determine the main effect of opium addiction on post-MI arrhythmias, prospective studies are recommended.

In conclusion, the results showed that opium addiction is a potential risk factor for cardiac arrhythmias especially PVC and VT following AMI and the risk of this arrhythmia is higher in men than women.

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