IS OPIUM ADDICTION A RISK FACTOR FOR ACUTE MYOCARDIAL INFARCTION?

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Abstract- There is a misconception among our people that opioids may prevent or have ameliorating effects in the occurrence of cardiovascular diseases. In this study we evaluated 556 consecutive male patients hospitalized due to acute myocardial infarction (MI) in city of Yazd, from May 2000 to October 2001 and compared the characteristics of opium addicts to non opium users. Prevalence of opium addiction in MI patients was 19% in comparison with 2-2.8% in general population. There were not any differences in prevalence of traditional risk factors between opium users and non-users. Overall, in-hospital mortality was 18.6 percent among opium users and 6.2 percent among non-opium users (unadjusted odd ratio, 1.3; 95% confidence interval, 0.7 to 2.7, $P = 0.2$). After adjustment for the differences in the baseline features (age and other risk factors), odds ratio increased to 2.2 (95 percent confidence interval, 0.9 to 5.1). It seems that opium addiction may work as a risk factor in cardiovascular disease.

Acta Medica Iranica, 43(3): 218-222; 2005

Key words: Acute myocardial infarction, opium addiction, risk factor

INTRODUCTION

Opium abuse is a major problem for every society including our country. More than 180 million people have tried illegal drugs once and there are 13.5 million opium addicts in the world.

It is estimated that the prevalence of opium addiction has grown up by three folds for the past 20 years in Iran and now it is presumed to be 2-2.8% according to official address (1). It is estimated that there are 40000-50000 opium addicts in the city of Yazd. The annual financial burden of opium addiction exceeds 5 billion dollars in Iran. One of the reasons for this high prevalence is the misconception among our people that opioids may prevent or have ameliorating effects in the process of hypertension, diabetes mellitus and occurrence of cardiovascular diseases. We performed this study to establish the prevalence of opium addiction in patients with myocardial infarction (MI) and to compare the characteristics of opium addicts to non opium users.

Received: 31 Aug. 2004, Revised: 26 Oct. 2004, Accepted: 30 Oct. 2004

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MATERIALS AND METHODS

The studied population consisted of 556 consecutive male patients with MI admitted from May 2000 to October 2001 to coronary care unites (CCU) in the city of Yazd. Diagnosis of acute MI was confirmed based on serial ECG changes and enzyme analysis. For patients who fulfilled the criteria, questionnaires including demographic, clinical and paraclinical characteristics were completed. Hypertension was defined as the current use of antihypertensive medication or an average blood pressure >140/90 mmHg on two different occasions. Hyperlipidemia was defined by serum cholesterol level >200 mg/dl, serum triglyceride >200 mg/dl or use of antihyperlipidemia drugs. A

diagnosis of diabetes mellitus was made if the patient needed insulin, oral hypoglycemics or restriction of dietary sugar or had fasting blood glucose ≥ 126 mg/dl. A patient was defined as opium addicted if he had been using opium for at least 12 months prior to admission.

Statistical Analysis

All the analyses were performed with SPSS software, version 10. Fisher's exact and Chi square testes were used to determine the significance of the differences between proportions and a probability value of less or equal to 0.05 was considered significant. In-hospital mortality was compared between opium-users and non-users first without adjustment, then with adjustment for age and other covariates by means of multivariate stepwise logistic regression analyses. In each model tested, opioid addiction was forced into the model, whereas other predictors were selected in a stepwise manner. Results are presented as odds ratio with a 95 percent confidence intervals.

RESUTLS

Opium addicted patients made up 19% of the population. The mean age was 54.6 ± 11 years for opium users and 60.1 ± 12 years for non opium users. Table 1 shows the demographic and clinical characteristics of these groups. Educational attainment was lower in persons who used opium. No significant differences were found between opium users and non-users in any of the following characteristics: hypertension, diabetes mellitus, and hyperlipidemia. Persons who reported use of opium were more likely to be current cigarette smokers (87.5 vs 44.2, $P < 0.001$). The median time elapsed from the onset of symptoms to CCU admission was one hour longer in opium users compared to non opium users (7.2 vs 6.5), although this difference was not statistically significant ($P = 0.3$). Table 2 shows status of traditional risk factors of myocardial infarction in opium addicted patients. It doesn't show that traditional risk factors were more prevalent in opium addicted patients with the exception of diabetes mellitus.

Table 1. Baseline characteristics of patients according to opium usage*

Characteristics	Opium non-users	Opium users	*P*
Age (years)†	60.1±12	54.6±11	< 0.0001
Education			< 0.0001
Not educated	296 (52.4)	24 (26.4)	
Primary school	193 (34.2)	40 (44)	
High school	45 (8)	16 (17.6)	
Academic	31 (5.5)	11 (12.1)	
Marital status	363 (52.3)	78 (62.9)	0.005
Hypertension	144 (27.4)	30 (24.8)	0.3
Diabetes mellitus	119 (22.6)	30 (24.8)	0.3
Hyperlipidemia	144 (27.5)	37 (30.8)	0.2
Smoking status	231 (44.2)	106 (87.5)	< 0.0001
BMI (kg/m^2) †	25.1±3	25.3 ±4	0.9
Waist to hip ratio†	1±0.097	0.99±0.1	0.8
MI level			0.9
Inferior	164 (32.6)	27 (32.1)	
Septal	45 (8.9)	9 (10.7)	
Anterior	67 (13.3)	13 (15.5)	
Anteroseptal	122 (24.3)	20 (23.8)	
Killip class (I)	533 (89.1)	90 (90.9)	0.9

Abbreviations: BMI, body mass index; MI, myocardial infarction.
* Data are given as number (percent) unless specified otherwise.
† mean ± SD.

Overall in-hospital mortality was 18.6 percent among opium users and 6.2 percent among non opium users (P= 0.2).

Table 2. Status of risk factors in opium users before and after adjustment for age and smoking

Risk factors	Odds ratio	*P*
Hypertension		
Unadjusted	0.87 (0.5-1.3)	0.3
Adjusted for age	1.02 (0.6-1.6)	0.9
Adjusted for smoking and age	1.1 (0.6-1.8)	0.6
Diabetes mellitus		
Unadjusted	1.1 (0.7-1.7)	0.3
Adjusted for age	1.2 (0.7-1.9)	0.4
Adjusted for smoking and age	1.4 (0.8-2.3)	0.1
Hyperlipidemia		
Unadjusted	1.17 (0.7-1.8)	0.2
Adjusted for age	1.16 (0.7-1.8)	0.4
Adjusted for smoking and age	1.3(0.8-2.2)	0.1

Table 3. Comparison of in-hospital mortality among opium addicted patients before and after adjustment for covariates

Adjusted for	Odds ratio	*P*
Unadjusted	1.3 (0.7-2.7)	0.2
Adjusted for diabetes mellitus	1.4 (0.7-2.8)	0.3
Adjusted for smoking	1.7 (0.7-3.9)	0.1
Adjusted for smoking and diabetes	1.7 (0.7-3.8)	0.1
Adjusted for smoking and diabetes and age group	2.2 (0.9-5.10	0.057

The unadjusted odd ratio for death among opium users compared to non opium users was 1.3 (95 percent confidence interval, 0.7 to 2.7, Table 3). In-hospital mortality was 4.6 percent among smokers and 9.7 percent among non smokers. It is suggested that the difference in the mortality reflects the difference in smoking status between opium users and non-users presented with acute myocardial infarction. Adjustment for smoking increased the odd ratio to 1.7 (95 percent confidence interval, 0.7 to 3.9).

In-hospital mortality was 2.2 fold in diabetic patients compared to non-diabetics (15.5 vs 7.4, $P < 0.0001$). We adjusted in-hospital mortality for this factor and odd ratio increase to 1.4 (95 percent confidence interval, 0.7 to 2.8). Adjustment for other differences in the baseline features (age and risk factors) in the logistic regression model produced a further moderate increase in the odd ratio to 2.2 (95 percent confidence interval, 0.9 to 5.1).

DISCUSSION

The word opium is derived from the Greek name for juice, the drug being obtained from the juice of the poppy; papaver somniferum (2). A 1997 national survey reported that almost 5% of men and women aged 12 or above in the United States had used an opioid for intoxication, including almost 2% in the prior year and slightly less than 1% in the prior month (3). In Iran, prevalence of opium addiction is almost 2-2.8 percent in general population, but it was about 19% in our population with myocardial infarction.

In our population one of the current incentives for opium abuse is suggested to be fear of myocardial infarction. Therefor we excluded patients that had another infarction; now in new population, prevalence of opium addiction was 14.4 percent. This higher prevalence of addiction among MI patients compared to estimated total prevalence in the general population points out to the relation of addiction and myocardial infarction (14.4 VS8%). What are the reasons? Does addiction work as a reason or result? Do opium addicts have specific lifestyle? Is opium a risk factor for coronary heart disease?

There is a misconception in the mind of our people that opium has ameliorating effects on hypertension, diabetes mellitus and cardiovascular events. However, we didn't find any difference in the prevalence of risk factors between two groups. Whereas, these patients didn't have higher prevalence of cardiac risk factors, myocardial infarction occurred in those that had younger age. Another issue to be considered is the higher prevalence of mortality in opium users. In hospital-mortality was higher among opium-users than non-users. Also, the mean time elapsed from the onset of symptoms to CCU admission was one-hour longer in opium users. It suggested that opium masked the symptoms of patients, but 96 percent of opium users suffered from chest pain before admission against 96.3 percent among non opium users ($P = 0.5$).

Another issue that needs to be considered is thrombolytic therapy in these two groups; 60.4% of opium users and 56.4% of non opium users received thrombolytic therapy, a difference that was not statistically significant ($P = 0.2$). Other factors that influence the mortality such as level of MI Killip class, treatment by β blocker and aspirin didn't show difference between two groups.

Thus, addiction may act as a risk factor for coronary heart disease. Opioids act in the hypothalamus to inhibit the release of gonadotropin-releasing factor (GnRH), thus decreasing circulating concentration of luteinizing hormone (LH) and follicular-stimulating factor (FSH). As a result of the decreased concentration of pituitary trophic hormones, the concentrations of testosterone in plasma declines (4). Men with coronary heart disease have been shown to have low levels of plasma testosterone. Testosterone is structurally similar to estrogen, although the sexual effects of these

hormones are very different, they may have similar effects on the vasculature (5). In men without prior myocardial infarction who were referred for coronary angiography, a significant inverse correlation has been found between plasma testosterone levels and the extent of coronary artery disease, demonstrating that men with low testosterone levels may be at an increased risk for coronary atherosclerosis (6).

The direct effect of testosterone on coronary circulation in men is unknown. Testosterone induces relaxation in preconstructed rabbit coronary artery and aorta *in vitro*, with or without endothelium (7, 8). Testosterone is converted to 17 β-estradiol by the enzyme aromatase. It is possible that estradiol may account for the vascular effects of testosterone; however, the evidence to date does not support this potential mechanism. Carolyn *et al*. demonstrated direct coronary effects of testosterone at physiological concentration (adult male normal range is ~10-9 to 10-8 mol/l) in humans (9). They reinforced the observation of Phillips *et al.* that low plasma testosterone may be a risk factor for coronary heart disease. Opium peptides and exogenous opioids such as morphine are known to exert important cardiovascular effect.

Recent data have revealed that opioid peptides are involved in the phenomenon termed cardiac preconditioning. Preconditioning is the ability of a short insult (ischemia or hypoxia) to protect the heart from damage due to subsequent prolonged insult. The result is a smaller infarct size in proportion to the area at risk (10). Schultz *et al.* demonstrated that induction of preconditioning with morphine and d1-opioid receptor agonist further proved that endogenous opioid peptides are involved in preconditioning in rats (11, 12). However, in our study, we didn't find any difference in the ejection fraction between two groups (44 vs 45, $P = 0.4$). Selective delta specific agonists such as 2-methyl-4a-alpha- (3-hydroxyphenyl)-1,2,3,4,4a,5,12,12a-alpha-octahydroquinolino[2,3,3-g] isoquinoline have been shown to exert potent cardioprotective effects in intact animals and cardiac myocytes via activation of Gi/O proteins, protein kinase C, and ultimately, the mitochondrial KATP channel (13).

Opium is not a pure substance. The alkaloids constitute about 25% by weight of opium and can be divided into two distinct chemical classes, phenanthrene and benzylisoquinolines. The principal phenanthrenes are morphine (10% of opium), codeine (0.5%) and thebaine (0.2%). The principal benzylisoquinolines are papaverine (1%), which is a smooth muscle relaxant, and noscapine (14). The exact action of this substance is not clear. On the other hand, the usual route of usage in our society is smoking opium. Opium smoke is inhaled by addicts after it has been burned on special instruments. Do this smoke and its components have adverse effects on cardiovascular system? We recommend that similar studies should be conducted to evaluate the status of opium addicted patients and their outcome regarding myocardial infarction. The present paper has opened the question of negative effect of opium addiction on MI patients. More clarification of issue has important social, cultural and financial influences on our society. Opium abuse is a major problem for every society. It seems that opium addiction is more prevalent in MI patient than in general population. The prevalence of traditional risk factors was not statistically different between addicted and non-addicted patient. In –hospital mortality was higher among addicted patients even after adjustment for factors that have influence on mortality. But we believe that for better decision making a more comprehensive study with follow up of patients should be carried out in this context.

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