Original Article

Opium Decreases the Age at Myocardial Infarction and Sudden Cardiac Death: A Long- and Short-term Outcome Evaluation

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Abstract

Background: Opium dependence is a recognized individual and public health threat, but little is known about its association with acute myocardial infarction (AMI) or sudden cardiac death (SCD).

Methods: In a cross-sectional study followed by a one-year matched longitudinal cohort, all 569 men hospitalized with AMI in all Cardiac Care Units (CCU) of Isfahan, Iran, were recruited in a six-month period. In addition, 121 out-of-hospital deaths were included that were diagnosed as SCD at the same duration. Among those discharged alive, 126 opium dependents were matched with 126 nondependents (mostly nonusers) according to age and smoking status, and were followed for one year. Opium dependence was measured using the ICD10 criteria and Severity of Dependence Scale (SDS) questionnaire. The method was validated by morphine blood levels. Biochemical measurements, blood pressure, blood cell counts, anthropometrics, and ejection fraction were measured at baseline and repeated at the end of follow-up.

Results: There were 118 (17.1%) patients with an average of 17.4 ± 10.4 years of abuse who met the criteria for opium dependency. Opium dependence decreased the age at event by 3.6 (95% CI: 1.2 – 6.0) years and was independent of smoking ($P = 0.003$). In terms of cardiovascular risk factors and ejection fraction, in addition to post-AMI mortality and morbidity, no significant associations were noted at baseline or after one year of follow-up. The odds ratio of sustained smoking after AMI was 1.92 (95% CI: 1.04 – 3.52) in opium dependents ($P = 0.033$).

Conclusion: Despite public opinion, opium did not improve cardiovascular risk factors, or post-AMI mortality and morbidity. Conversely, there were irrefutable findings regarding the detrimental effects of opium dependence.

Keywords: Complications, myocardial infarction, opium dependence, risk factor, sudden cardiac death

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Introduction

Iran is located in the main pathway of opium transit and its people are among the largest consumers of opium worldwide.[1] Opium is the first-rated substance of abuse in Iran.[2,4] Although a nationwide statistical survey of opium consumption in the Iranian population is missing, it has been estimated that the prevalence of opiate addiction has risen by three-fold during the last 20 years, reaching 2% – 2.8%, according to government reports.[3] Available data show that more than 90% of addicts are males.[4]

For thousands of years, opium has been called balm in the Middle East and most likely in other regions. The analgesic effect of morphine, the main ingredient of opium, explains this traditional belief to some extent but only justifies limited use of opium. On the other hand, patients have attained a gradual awareness of pharmaceutical products that contain morphine and are widely used in cardiac settings. Seemingly, these have led to a misunderstanding in the public that the analgesic effect can be generalized to other situations such as ischemic heart diseases (IHD) and their risk factors, even in the absence of pain. Although there is insufficient supporting evidence, some healthcare professionals in Middle Eastern countries believe that opium ameliorates some of the risk factors of IHD. Recent developments in economy and transportation have greatly facilitated the illegal business of opium throughout the world. In addition, recreational purpose is a well-known strong motivation for opium use. Overall, in addition to the psychological factors, these form a considerable motivation for the tendency towards opium use, which in most cases results in opium dependence.

Opium is a variable mixture of substances that extensively impact the cardiovascular system.[5,6] After accidents, suicide, and cancers the most common cause of death in opioid addicts was reported to be IHD.[7] Opium addiction is by far more prevalent in IHD patients.[8,9] Some studies have reported worsening or null effects of opium or opiates on traditional risk factors,[7,9–15] whereas others have found opium to be beneficial for the prevention of IHD.[16–19]

This study aimed to investigate the prevalence of opium dependence in men with acute myocardial infarction (AMI), to compare the characteristics of two groups of patients with or without opium dependence, and to compare short-and long-term morbidity and mortality following AMI.

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Materials and Methods

In a cross-sectional study, all AMIs and sudden cardiac deaths (SCD) that occurred among men in Isfahan in 2006 were investigated using the census sampling method (prevalence study). A matched cohort of opium dependents with nondependents were followed for more than one year post-AMI (follow-up study).

Prevalence Study

The study protocol was reviewed and approved by the Isfahan Cardiovascular Research Institute Review Board/Ethics Committee, affiliated with Isfahan University of Medical Sciences. All phases of the study were designed and performed with regard to the Declaration of Helsinki. Patients or their close families were provided with information about the goals of the study and were assured of confidentiality. Written informed consent was obtained from all subjects or the family of the deceased.

All male subjects admitted to emergency departments of all 13 hospitals that had Cardiac Care Units (CCU) in Isfahan and who were diagnosed with AMI based on the American College of Cardiology/American Heart Association Guidelines,[20] as well as those who sought Emergency Medical Service (EMS) but died at home or before the determination of a diagnosis in the Emergency Department were included in the study.

Although recruitment was conducted over a six-month period, it was continued in certain hospitals until the required sample size for the second phase was reached. We calculated that 121 subjects in each group would be required to detect a difference of at least 20% (effect size) in post-AMI complications between the two groups, with a power of 90% ($\beta = 0.1$) at the two-tailed 0.025 level of significance ($\alpha = 0.05$) and an estimated proportion of 30% for outcome of interest in one group and maximum (50%) in the another group. Since the diagnoses of AMI were made by different cardiologists in different hospitals, diagnostic information from all cases was reviewed by a trained cardiologist (third author) throughout the study and only confirmed cases were included.

Structured interviews based on a designed questionnaire were administered by a trained CCU nurse in each hospital within the first 24 hours after admission. Patients were observed by the corresponding nurse at each hospital until discharge; all short-term complications or mortality were recorded. In terms of patients who expired in the hospital before being interviewed, a telephone call to interview their family was arranged within one month after death. A brief interview that included necessary information was conducted.

Demographics, level of education, income status, and smoking behavior were questioned; systolic and diastolic blood pressures of the patients on admission were recorded. Anthropometrics that included body weight, height, and waist circumference (WC) were measured by standard methods as soon as hemodynamic stability was maintained. Biochemical findings, blood cell count, and echocardiographic data were also collected from patients' records. Smoking status was categorized as nonsmoker (those who never smoked or who had not smoked for at least two years), smokers (one to 20 cigarettes per day) and heavy-smokers (> 20 cigarettes per day). No case of occasional smoking was reported.

Opium consumption was evaluated based on the ICD-10 criteria for opioid dependence which included duration, amount, and route of consumption. A nine-item questionnaire based on ICD-10 criteria was used.[21,22] The topics of questions consisted of cravings, difficulties in controlling use, withdrawal symptoms, tolerance, neglecting activities, negative consequences, and experiences of psychological or physical harm. The quality of interviews was supervised monthly by a psychiatrist. Anyone who had at least three of these nine conditions or used opium ≥ 3 times a week was defined as opium dependent. Reliability and validity of the questionnaire were measured in a pilot study. The internal consistency and factor structure of the questionnaire were assessed through Cronbach's alpha and calculated as 0.86. Validity of this method was investigated by blood test using an automated microplate enzyme immunoassay at a cutoff of 20 ng/mL morphine as the gold standard.[23] It resulted in a sensitivity of 83.3% and specificity of 79.4%. The Severity of Dependence Scale (SDS) questionnaire[24] was also completed for patients who had reported opium consumption.

In terms of out-of-hospital deaths, all EMS recordings registered during the six-month period of the study were reviewed using the database at the Isfahan EMS Headquarters. Patients who experienced trauma and those who died of a distinctive noncardiac cause were excluded. A verbal autopsy interview with family members of the deceased was performed by a trained nurse for each death report and reviewed by a cardiologist in order to make a diagnosis of SCD. SCD was labeled as an unexpected death that occurred out of hospital within 24 hours of the first symptom(s) if no other obvious cause of death such as other serious life-threatening diseases were proposed.

Follow-up Study

Among men who were recruited in survey data, 126 nondependent patients were selected as the unexposed group and individually matched with all 126 opium dependents that were discharged alive after AMI. Matching was undertaken monthly based on smoking status and age (±3 years) among patients of the same hospital, as best as possible. If there were more than one matched candidate for an opium dependent, one was randomly selected.

Six months after admission of each pair, telephone interviews were performed to obtain information about mortality and morbidity that included additional hospitalizations, doctor visits, unemployment, and Canadian Cardiovascular Society (CCS) angina classification.[25] After one year of follow-up, the participants were invited to the clinic where they were interviewed using the same questionnaire. Blood pressure and anthropometrics were measured by standard methods and a fasting blood sample was obtained to measure biochemical factors, blood cell counts, Apo A, and Apo B levels. Echocardiography was performed for all participants by a cardiologist. Patients were requested to bring all their medical records including procedures and relevant paraclinical measures. In terms of mortality, patient records were retrieved from hospitals. In cases that no record was available or it was impossible to be retrieved, a verbal autopsy was performed. Verbal autopsy was a structural interview by witnesses or close relatives regarding the circumstances and symptoms that resulted in death. Verbal autopsies were carried out by a trained nurse. A cardiologist made the final diagnosis based on this information.

Knowledge and attitude of people regarding opium were extracted from the final survey database of the Isfahan Healthy Heart Program (IHHP). IHHP was a community trial that conducted annual surveys. It recruited participants from three areas using cluster random sampling. The detailed method has been described in an article published by Sarafzadegan, et al.[26] The extracted data were comprised of information from the same area as the main study (urban parts of Isfahan) and undertaken simultaneously (2006).

Statistical Analysis

Data entry was carried out by using EPI Info™. Data were analyzed using SPSS (SPSS Inc., Chicago, IL, USA; version 15) and Stata (Stata/IC 11.0, StataCorp LP, TX, USA). Student's t-test was employed for the comparison of means of the independent groups and the χ^2 test for the comparison of proportions. Paired t-test was used to compare age at onset of smoking with age at onset of opium consumption. Normality was checked graphically and logarithmic transformation used for fasting plasma glucose and triglyceride levels, in addition to family size because of positive skewness. In terms of ordinal values of the CCS angina classification, the nonparametric Mann-Whitney test was used.

The general linear model (GLM) was employed to the compare age of opium dependent subjects with the remainder of participants with regards to smoking status. In the survey data, multiple linear regression was applied to assess the effect of opium dependence (independent variable) on the age at which AMI occurred (dependent variable), adjusted for other risk factors. The effect of opium dependence on post-AMI events (death and hospitalization) was investigated using conditional Cox regression applied to one year survival data and matched based on age and smoking status.[27] To compare smoking and opium use before and after AMI, McNemar test was performed. For all analyses, statistical significance was assessed at a level of 0.05 (two-tailed) and *P*-values from 0.05 to 0.1 were considered borderline significance.

Results

During a six-month period from December 1, 2006 through May 31, 2007, 569 men diagnosed as AMI were admitted to the hospitals in Isfahan. During the same period, 302 out-of-hospital deaths in men were documented as cardiac deaths in that area. However, close relatives of 234 (77.4%) deceased subjects could be contacted. The study cardiologist confirmed 121 cases as SCD, which brought the total events to 690. The average of age was 61.2 ± 13.1 years (range: 19 – 86). Opium consumption was reported by 159 (23.0%) patients or close relatives if the subject was deceased, from which 118 (17.1%) with an average of 17.4 ± 10.4 years of abuse were diagnosed as opium dependent. While the SDS score was 2.1 ± 2.3 in 29 (19.7%) nondependent opium users, it was 7.8 ± 3.8 in opium dependents (*P* < 0.001). Although less numbers of patients met the criteria for opium dependence based on information of close relatives of the deceased as obtained by verbal autopsy compared to alive patients (15.7% vs 17.4%), the difference was not statistically significant (*P* = 0.653).

Table 1 shows the differences in socioeconomic factors as well as cardiovascular disease risk factors between opium dependents and nondependents. There was no significant difference between both groups in most items, with the exception of age, smoking status, income, and white blood cell levels. The observed differences were investigated if AMI cases differed from SCDs, but no significant discrepancy was found (data not shown). Smoking was 33.2 (95% CI: 27.7 – 38.7) pack year higher in heavy smokers than smokers (45.7 ± 28.2 vs 12.5 ± 9.9, *P* < 0.001). Smoking increased the risk of opium dependence 5.1 (95% CI: 3.2 – 8.3) times. The age at which opium dependents began smoking was 12.2 (95% CI: 9.5 – 14.9) years before the age that they began to use opium (*P* < 0.001). The age that all participants began to smoke was 22.5 ± 8.8 years; however, the age of using opium for the first time was 36.4 ± 12.9 years (mean ± SD). Age at onset of smoking in opium dependents did not differ from others (*P* = 0.566).

The linear regression model showed that opium dependence decreased the age at which AMI or SCD occurred when adjusted for smoking, hospital, death or living status, and socioeconomic factors such as income, education, and family size. While smoking caused a 5.8-year (4.0 – 7.7) decrease in the age at event occurrence (*P* < 0.001), opium dependence independently decreased this by 3.6 (1.2 – 6.0) years (*P* = 0.003) [B coefficient (95% CI)]. This model described 30% of variation in the age at event variable (R2 coefficient of determination = 0.308). There was no significant interaction between smoking and opium dependence (*P* = 0.567). The independent decreasing effect of opium dependence on age of occurrence of the event remained significant when the severity of smoking was considered (Figure 1). Premature events (age < 45 years) were detected in 79 (11.4%) cases. While 22 (18.6%) premature events occurred in opium dependents, there were 57 (10%) events in the nondependent group (*P* = 0.007). However, this deleterious association was not significant (95% CI: OR = 1.2, 0.7 – 2.2, *P* = 0.380) when the confounding effect of smoking was taken into account (95% CI: OR = 4.5, 2.5 – 7.8, *P* < 0.001).

During nearly the same period, 2854 IHHP participants from the same area (urban Isfahan in 2006) were questioned about opium and smoking use. Regarding the effect of opium consumption, 628 (22.0%) participants thought that it reduces the risk of heart attack, 22.4% were uncertain, and 55.6% answered with certainty that opium does not reduce this risk. Concerning the effect of opium on reducing blood sugar, 911 (31.9%) believed that opium causes such a reduction, and 879 (30.8%) stated that opium reduces blood pressure. However, 2722 (95.4%) participants knew that active smoking increased the risk of cardiovascular events, whereas 2685 (94.1%) participants expressed awareness that passive smoking caused an increase in the risk of cardiovascular events.

For 126 opium dependents who were admitted and diagnosed with AMI, 126 nondependents were selected as the unexposed group and were followed for a median follow-up of 13 months. There were 14 (5.6%) patients, five (4.0%) nondependents and nine (7.1%) dependents, lost to follow- up, but the difference was not significant (*P* = 0.271). There were no significant differences in blood pressure, lipids, plasma glucose, BMI, and WC between these two groups, neither at baseline nor at the end of follow-up (data not shown). Apo B and Apo A were also measured at the end of follow-up but did not show a statistically significant difference. Overall, there were 30 deaths from which 18 were diagnosed as SCD. Table 2 shows the lack of significant differences between opium dependents and nondependents in terms of post-AMI mortality and morbidity. A composite variable that included death and hospitalization was also analyzed but no significant relationship was found (*P* = 0.376). Likewise, conditional Cox regression showed no age adjusted relationship between opium and mortality (HR = 0.61, 95% CI: 0.20 – 1.79, *P* = 0.374), hospitalization (HR = 1.27, 95% CI: 0.63 – 2.59, *P* = 0.494), and their combination (HR = 1.09, 95% CI: 0.63 – 1.89, *P* = 0.732).

During almost one year of follow-up, 64 (41.3%) smokers quit

Table 1. Characteristics of the participants who experienced acute myocardial infarction (AMI) or sudden cardiac death (SCD)

		Nondependents§	Opium dependents	*P*- value
		N = 572	N = 118	
AMI or SCD	Smoking (n%)	194 (34.8%)	86 (73.5%)	< 0.001
	Heavy smoking (n%)	101 (18.5%)	63 (54.8%)	< 0.001
	Age at onset of smoking (year)	22.7 ± 8.4	22.0 ± 9.2	0.566
	Age (year)			
	All	64.0 ± 13.0	56.5±12.2	
	Smokers	57.9 ± 12.6	55.2±12.3	< 0.001
	Non-smokers	67.1 ± 12.2	59.8±11.3	< 0.001
	Income (n%)*			0.029
	< 1000	61 (13.4%)	8 (8.5)	
	2000–1000	178 (39.1%)	30 (31.9%)	
	3000–2000	138 (30.3%)	28 (29.8%)	
	> 3000	78 (17.1%)	28 (29.8%)	
	Education (n%)			0.259
	Illiterate	129 (26.0%)	27 (25.5%)	
	Primary school	198 (39.9%)	38 (35.8%)	
	Secondary school	112 (22.6%)	33 (31.1%)	
	University	57 (11.5%)	8 (7.5%)	
	Family size	4.3±2.1	4.7 ± 2.1	0.084
	Mortality** (n%)	112 (19.6%)	20 (16.9%)	0.508
		N = 470	N = 99	
AMI	Alcohol consumption n (%)	28 (5.9%)	4 (4.0%)	0.300
	Waist circumference (cm)	96.1 ± 13.3	94.5 ± 12.0	0.312
	Body mass index (kg/m²)	25.5 ± 3.7	25.3 ± 3.7	0.713
	Triglycerides (mg/dL)	136.2 ± 95.4	153.5 ± 117.7	0.069
	Systolic blood pressure (mmHg)	134.3 ± 26.3	135.7 ± 28.2	0.638
	Diastolic blood pressure (mmHg)	83.6 ± 15.2	83.6 ± 18.1	0.979
	Total cholesterol (mg/dL)	195.3 ± 50.5	188.3 ± 53.8	0.278
	LDL-C (mg/dL)	123.9 ± 45.5	121.3 ± 44.1	0.671
	HDL-C (mg/dL)	39.6 ± 9.6	39.4 ± 10.8	0.885
	Fasting plasma glucose (mg/dL)	137.5 ± 65.7	135.9 ± 67.1	0.792
	White blood cell counts (μL)	9133 ± 3342	10245 ± 3606	0.004
	Red blood cell counts (×10⁶/μL)	4.9 ± 0.8	5.1 ± 1.8	0.281
	Platelet counts (×10³/μL)	209.6 ± 69.8	206.8 ± 65.7	0.720
	Hospital stay (days)	5.8 ± 2.2	5.8 ± 1.9	0.839
	Ejection fraction	42.5 ± 12.3	43.6 ± 10.7	0.453

Numerical factors are presented as mean ± SD; *Thousand rials; **Early in-hospital death and SCD; § Comprised of 543 nonusers and 29 nondependent opium abusers; AMI: Acute myocardial infarction; SCD: Sudden cardiac death.

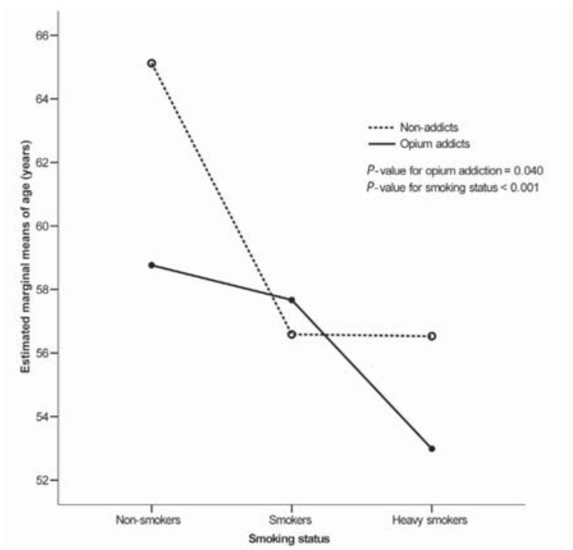

Figure 1. Age differences in opium dependents against smoking severity in patients who suffered from acute myocardial infarction (AMI) or sudden cardiac death (SCD)

smoking and five (10.2%) nonsmokers began to smoke (*P* < 0.001). The risk of continuing smoking after AMI was 92% more (OR = 1.92, 95% CI: 1.04 – 3.52) in opium dependents compared to nondependents (*P* = 0.033). Although 18 (16.8%) opium users stopped, 10 (10.4%) nonusers began to use opium after AMI. However, these changes were not statistically significant (*P* = 0.185).

Discussion

Opium dependence was found in 17.1% of men who suffered from AMI or SCD and resulted in cardiovascular events at a lower age, even when smoking was considered. Smoking strongly increased the risk of opium dependence, which on average happened 12 years after the onset of smoking. One-fifth of the general

Table 2. Comparison between opium dependents and nondependents after one year of follow-up following acute myocardial infarction (AMI)

		Nondependents§	Opium dependents	*P*- value
		N = 126	**N = 126**	
Baseline*	**Age (mean ± SD)**	57.1 ± 11.9	54.4 ± 11.5	0.070
	Smoking (n%)			
	None	31 (24.6%)	30 (23.8%)	0.988
	Moderate	25 (19.8%)	25 (19.8%)	
	Heavy	70 (55.6%)	71 (56.3%)	
		N = 121	**N = 117**	
Outcomes	**Mortality (n%)**	16 (13.2%)	14 (12.0%)	0.770
	Sudden cardiac death (n%)	8 (6.3%)	10 (7.9%)	0.625
	Hospitalization (n%)	35 (27.8%)	42 (33.3%)	0.338
	Six-month CCS angina classification	94.8 †	99.1†	0.576
	One-year CCS angina classification	85.6 †	95.7†	0.167
	Doctor visits (mean ± SD)	5.6 ± 3.9	5.3 ± 3.5	0.592
	Unemployment (n%)	19 (20.9%)	17 (19.1%)	0.766
	Ejection fraction (mean ± SD)	48.7 ± 10.1	44.9 ± 10.1	0.080

* Matching items; § comprised of 116 nonusers and 10 nondependent opium abusers; † Mean rank.

population believed that opium dependence decreased the risk of heart attack and one-third believed it to have a beneficial effect for hypertension and diabetes. Despite public opinion, no preventive effect was found for opium in this study, neither for cardiovascular events or risk factors nor for post-AMI mortality and morbidity. On the other hand, opium dependents were less likely to quit smoking after AMI. After a median follow-up period of 13 months, opium-dependent patients had similar post-AMI morbidity and mortality compared with nondependents.

Interestingly, opium consumption was more prevalent in IHD patients. Previous limited observations estimated the prevalence at 10% in coronary artery bypass graft patients[8] to as high as 19% in patients with AMI.[9] In this study, the rate of concurrent opium consumption was 23% in male AMI patients (opium dependence, 17.1%). A recent report from northern Iran reported the opium use rate to be 17% in the general population and showed its detrimental effect on IHD risk and certain other diseases.[15] Here, however, a dilemma exists. Since it is generally believed that drug abuse is connected with poor general and mental health status,[28] opium consumption may be propounded as a behavioral risk factor rather than an independent one. Some findings have supported this hypothesis. Smoking and opium abuse were strongly related in our study and opium dependents hardly quit smoking. Drug users were more likely to have an inappropriate dietary pattern.[29]

Consistent with other studies,[30,31] our report showed strong belief by the public regarding the possible beneficial effects of opium consumption. This idea inevitably will encourage some patients to use opium. Although there is a consensus about the beneficial effects of the therapeutic use of opioids after AMI,[32] a paucity of the literature has explored the consequences of their chronic use. Long-term use of opiates, however, has shown some cardioprotective properties in animal studies. A number of mechanisms have been suggested to explain these observations, such as ischemic preconditioning.[16,17,19] In a cross-sectional study on Iranian truck drivers, opium-addict participants were found to have significantly lower diastolic blood pressure and total cholesterol levels.[18] The majority of published records, including ours, were not concordant with the abovementioned results.[7,9,11] We did not find any beneficial effect of chronic opium consumption on traditional risk factors in AMI patients. More than the null effect found in our study, significant deleterious effects of opium on some traditional and new cardiovascular risk factors such as HDL-cholesterol,[10,12,13] blood pressure,[13] glycosylated Hb, Lp(a), CRP, Apo B, ALT, and AST[10] have been reported in previous studies. Nonetheless, most of these studies had non-negligible limitations such as haphazard sampling methods, thus there is still a great deal of controversy in this field.

As with our findings, the independent decreasing effect of opium dependence on AMI age has also been shown by Sadr-Bafghi and colleagues.[9] This finding could be considered as a clue for the possible influence of opium on the process of atherosclerosis. Some properties of opiates are supposed to play a role in this process. Opiates have been shown to cause decreases in plasma testosterone levels by inhibiting the secretion of gonadotropin releasing hormone (GnRH).[33] Plasma testosterone level has a significant inverse correlation with the extent of CAD.[34] Increases in plasma levels of adrenalin, noradrenalin, corticosterone, and glucagon are among the other endocrine effects of this family of drugs.[12] These substances have a depressing effect on the autonomic nervous system, resulting in decreased enkephalin production in cardiomyocytes.[35] Influencing the inflammatory processes is another plausible mechanism. According to our results, opium-dependent patients had significantly higher WBC counts on admission. Leukocyte count is a marker of inflammation and the pivotal role of inflammation in progression of atherosclerosis is well established.[36] A number of observational studies have demonstrated that total WBC count during the acute phase of infarction is a prognostic indicator for adverse cardiovascular outcomes.[37] However, the clinical significance of each of the aforementioned effects has yet to be determined.

Our study did not find any cardioprotective effects of chronic opium consumption after AMI, which have agreed with the results of two independent studies on cardiac surgery and AMI patients.[2,38] However, since the beneficial effects of smoking cessation after AMI are well-known,[39-41] our finding regarding the lessened possibility of smoking cessation in opium dependents has suggested a strong indirect detrimental effect on post-AMI events that could be as high as a 56% risk increase in all-cause mortality.[41] On the other hand, age is a strong predictor of post-AMI mortality and morbidity.[42] In this study, the two groups in longitudinal phase were matched for age. In the prevalence phase, lower short-term complications were expected in opium dependents with 7.5 years younger age. As such effect was not observed, this similarity could also be a sign of the deleterious effects of opium dependence.

Our study findings had the following limitations. First, analyses of consensus data were cross-sectional, therefore we were unable to address causal relations. In addition, this study did not measure lifestyle factors such as physical activity, nutrition, and psychological stress. Third, conducting a survey in 13 hospitals inevitably could lead to problems such as differences in biochemical measurements. However, these centers had to comply with similar standards. Fourth, verbal autopsy reports obtained from relatives of the deceased is not inherently as accurate as direct interviews with patients themselves. With respect to the social stigma attached to opium dependence, prestige bias could decrease the reliability of information that was collected through verbal autopsy reports, particularly in terms of opium as well as alcohol use. Sixth, there might be some deaths that were not reported to EMS and were not included in this study. Finally, this study was not powered to report an association between opium dependence and post-AMI mortality and morbidity for differences of less than 20%. The consensus survey included all AMI events and premature AMI was a subgroup. There might be a lack of power to find an association between opium dependence and premature events when smoking was considered. We recommend future studies to address these issues, particularly in terms of longer follow-up periods and larger sample of premature AMI.

The consensus sampling method was the most important strength of this study that in addition to providing a large sample size, probably controlled selection bias. We validated our method for determining opium dependence in this study; there was acceptable sensitivity and specificity also applicable to deceased subjects. Finally, including SCD in addition to AMI led to better coverage and was itself a distinct strength of this study.

In conclusion, despite public opinion, opium not only failed to improve cardiovascular risk factors as well as post-AMI mortality and morbidity, but also decreased the age at occurrence and increased the risk of continued smoking after AMI. These findings in addition to the high prevalence of opium dependence in AMI patients suggest it to be a possible new independent risk factor for premature IHD. Such association should be further investigated in longitudinal studies, especially considering the role of lifestyle factors such as physical activity. Meanwhile, these findings stress the need for considering increased IHD risk in opium-dependent patients.

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Author contribution

The idea of this project was developed by HR and NS. The project was designed by MT and HR. Data gathering was managed by HR and MT with the assistance of PH. MS was in charge of diagnoses. Statistical analysis was performed by MT. The first draft was written by MT and HR with assistance by PS. NS supervised the entire project and revised the manuscript. All authors read and approved the manuscript.

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