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Original Article

Opium Addiction and Correlation with Early and Six-month Outcomes of Presenting with ST Elevation Myocardial Infarction Treated Initially with Thrombolytic Therapy

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Abstract: Background: Myocardial infarction is one of the most important causes of mortality worldwide. The role of opium addiction in the outcome of myocardial infarction is not known with many unproven beliefs surrounding it. This study was designed to evaluate the effects of opium addiction on in-hospital and six-month outcomes of patients presenting with ST elevation myocardial infarction (STEMI). Methods: This study was performed on STEMI patients who were initially treated medically in two hospitals without any primary percutaneous coronary intervention (PCI) facility. A total 117 opium addicted patients and 217 non-opium-addicted controls were followed during hospitalization and six months thereafter. The primary endpoint of this study was the in-hospital composite of death, heart failure, recurrent chest pain, and recurrent STEMI. Results: The composite endpoint was not significantly different either in-hospital or after six-month follow up (RR=0.851, 95% CI: 0.578-1.253 and RR=0.899, 95% CI: 0.578-1.253 relatively). Multivariate analysis also confirmed that opium addiction was not a predictor of in-hospital or six-month adverse outcome. Conclusion: The present study revealed that in-hospital and six-month adverse outcomes in opium addicted patients presenting with STEMI were not significantly different in comparison to patients without any opium addiction.

Keywords: Opium, narcotics, ST elevation myocardial infarction, coronary artery disease, myocardial infarction, acute coronary syndrome, addiction

Introduction

Opium addiction is a major issue of public health in some Eastern countries [1]. Opium is a complex mixture of different substances (e.g. morphine, codeine, thebaine, papaverine, etc.), obtained from the juice of the poppy plan botanically known as Papaver somniferum [2]. Different preparations named “Teriak, Sukhteh and Shireh”. are known. The milky fluid driven from incised poppy capsules makes the latex opium, known as “Teriak” after it dries in air. Teriak is used as inhalation by a hot stick or a specific pipe device namely “Vafoor” [3].

The are some beliefs in the population that opium could be beneficial for health in terms of reducing the risk of diabetes mellitus, hepertension and hyperlipidemia [4]. Opium is thought to be the most commonly abused substance in Iran [1] (after tobacco) [4]. Although, World Health Organization (WHO) has estimated the overall prevalence of drug abuse among the Iranian population to be 3.32 for men and 0. 55 for women [5]. Prevalence has been estimated to be as higher as 22.5% [1] and 26.5% [6] in the rural area.

Hypotension, bradycardia, and peripheral vasodilatation are among the important cardiovascular effects of opioids [7, 8]. Different reports from cross-sectional or case control studies suggest that opium consumption might be considered a risk factor for coronary artery disease

(CAD) [9-13]. Currently, the strongest evidence about the effect of opium on mortality comes from Golestan cohort estimating an 86% increased risk of death related to any opium consumption [3]. However, there is some evidence that morphine may have a cardio-protective effect immediately after administration [14] which is not the same as opium addiction. Furthermore, there are reports of better ST elevation resolution in response to fibrinolytic therapy among opium-addicted patients presenting with STEMI [15, 16].

Based on the above mentioned uncertainties regarding negative or positive effects of opium addiction on the cardiovascular system, we performed a largest study to date to evaluate the in-hospital and six-month outcomes of opium addicted patients presenting with STEMI initially treated with thrombolytic.

Methods

The study was an observational study of patients presenting with acute STEMI (Apr 2010-Dec 2012) in two hospitals with available coronary care units in Shahrood, Iran. Inclusion and exclusion criterion were as following: Inclusion were patients who were diagnosed as a new STEMI and were willing to sign the written informed consent. Excluded were patients who refused to sign the written informed or had Left bundle branch block, Left ventricular hypertrophy or ventricular paced rhythm on their presenting EKG. Exclusions based on EKG described above were based on uncertainties that could make STEMI diagnosis inaccurate. As there was no facility for primary PCI in the city, patients were medically treated according to the existing guidelines. Fibrinolytic therapy with streptokinase was administered according to the current recommendations unless contraindicated. After the streptokinase treatment, further care would depend on the streptokinase success. Patients without ST resolution and persistent chest pain would be transferred for rescue PCI. Patients with response to thrombolytic would undergo elective cardiac catherization based on the indications and patient's preference.

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 [17]. The patients were assumed opium addict if they fulfilled the criteria of regular consumption of oral daily opium or using it more than three times per week as inhalation [18].

The initial 12-lead ECG was obtained at the emergency room as soon as possible. Heart rate, systolic and diastolic blood pressures and creatine phosphokinase type MB (CKMB) were measured at the time of admission. Trans-thoracic echocardiography was performed in all patients within three days of admission blinded to the specific enrolment group.

Patients were monitored during hospitalization and 316 of the 334 patients completed the six-month follow-up. Our primary endpoint was composed of death, recurrent STEMI, any recurrence of ischemic chest pain with dynamic ST changes or dynamic T wave inversion, pulmonary edema or overt decompensated heart failure. The secondary endpoint was the above-mentioned composite outcome at the six-month follow-up.

The study protocol was approved by the local ethical committee and written informed consents were obtained.

Statistical method, sample size calculation and data analysis

Based on a pilot study of 20 patients, assuming the occurrence of a 20% in-hospital endpoint, with the prevalence of 30% addiction in our patients, with an α error of 0.05 and a power of 80%, we would need about 108 patients in the opium-addicted and 216 patients in the non-opium-addicted groups, in order to power our study appropriately. Finally, 117 patients were enrolled in "the opium-addicted group" and 217 patients in the "non-opium-addicted group".

The statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, Illinois) was used for analysis. 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 percentile] if they did not; categorical variables are summarized by raw numbers and percentages.

Continuous variables were compared using Student's t-test if they had normal distribution

or by a nonparametric Mann-Whitney U test whenever feasible. Categorical variables were compared using the chi-square or Fisher's exact test, as required. Relative risks (RR) and 95% confidence intervals (95% CI) were calculated for the primary and secondary endpoints. Logistic regression analysis was performed to eliminate the possible effect of the most important presumed clinical confounders on in-hospital and 6-month composite endpoints. These confounders included: sex, age, cigarette smoking, hypertension, diabetes mellitus, hyperlipidemia, and pretreatment with ASA. Kaplan-Meier curves were generated for 6-months follow up. A *p* value of <0.05 was accepted as statistically significant.

Results

The mean age of the study group was 59.62 ± 13.03 years and 252 (75.4%) were male. Opium-addicted patients were using opium for a mean duration of 14.32 ± 8.79 years. The mean usage of opium addiction was 1.16 ± 0.61 servings/day and they consumed 6487 ± 6182 servings/year of opium. In total, 98 patients (83.76%) used ≥1 serving/day.

The opium usage methods included inhalation (82.05%), oral (10.26%), and oral or inhalation (7.69%). Smoking inhalation was performed mostly with a hot stick (87.1%), and only 2.6% used "Vafoor".

The baseline characteristics of the opium-addicted and non-addicted groups are given in **Table 1**. The results of angiography and treatment options for those who performed angiography are also provided in **Table 1**. Among the referred patients for angiography, 210 patients (62.87%) completed invasive investigation and treatment. CABG was performed in 45 (32.6%) of non-opium addicted group and 13 (18.1%) of opium addicted vs. 93 (67.4%) of PCI or medical treatment in non-addicted and 59 (81.9%) in addicted patients respectively (P=0.025).

The in-hospital composite endpoints and death were seen in 89 (26.49%) and 17 (5.05%) of the patients, respectively. A comparison of outcomes during hospitalization, the hospitalization length, and ejection fraction before discharge in the two groups are presented in **Table 2**. Furthermore, six months follow up in opium addicted and non-addicted patients with STEMI are shown in **Table 3.**

Figure 1 shows the Kaplan-Meier curves of the six-month composite endpoint (A) and death (B).

The estimated relative risk for our in-hospital composite end point and 6-month follow up of opium consumption were 0.851; 95% CI: 0.578-1.253, (**Table 2**) and 0.899; 95% CI: 0.578-1.253 (**Table 3**) respectively. Furthermore, after adjustment for clinical confounders including sex, age, cigarette smoking, hypertension, diabetes mellitus, hyperlipidemia, and previous ASA intake, opium addiction was not a significant predictor of both in-hospital and 6-month composite endpoint (**Table 4**).

In-hospital and six-month composite endpoints were seen in 24 (22.9%) and 56 (59.6%) of inhalation opium users, versus four (33.3%) and six (50%) of oral-only opium users (P>0.05). Among opium-addicted patients with encountered in-hospital endpoints, opium consumption was 4690 [2646, 7300], with a mean of 5900 servings/year, in comparison to 5475 [2555, 9750], with a mean of 6672 servings/year in those without (P=0.949). For those with six-month endpoints opium had been consumed 5000 [2646, 7300], (mean: 5738) serving/year in comparison to 5475 [1956, 10950], (mean: 6903), serving/year was reported (P= 0.954). **Table 4** shows the results of logistic regression analysis for possible confounders of the effect of opium usage on composite endpoints. Figure shows Caplan mayor outcome curve.

Discussion

Opium addiction may have an effect on the markers of inflammation [11, 19] (e.g. CRP [8, 19]) and coagulation (e.g. Factor VII, and fibrinogen [19]). Opium-addicted patients may be more resistant to aspirin [20], have more arrhythmia after STEMI (mostly premature ventricular beats) [21], and may have less compliance with medical and dietary recommendations [22] that could affect their outcomes. In a large prospective study of 50,045 participants aged 40-75 at baseline (the mean age 52.1 ± 8.9 years) with a reported opium use of 17%, a significant association was seen between

Table 1. Baseline characteristics and the results of angiography and treatments performed after angiography in opium-addicted and non-addicted patients with ST elevation myocardial infarction

Variable	Opium addicted n=117	Opium non-addicted n=217	*P* Value
Sex (male)	106 (90.6)	146 (67.3)	<0.001
Cigarette smoking	77 (65.4)	40 (18.4)	<0.001
Hypertension	31 (26.5)	84 (38.7)	0.025
Diabetes mellitus	10 (8.5)	54 (24.9)	<0.001
Hyperlipidemia	10 (8.5)	45 (20.7)	0.004
Family history of CAD	26 (22.8)	42 (19.8)	0.526
Living in rural area	51 (43.6)	74 (34.1)	0.087
Past history of angina	30 (33.0)	68 (37.8)	0.436
Past history of STEMI	1 (0.9)	4 (1.9)	0.660
Past history of CABG	0	3 (1.4)	0.555
Past history of PCI	5 (4.3)	5 (2.3)	0.330
Past history of CVA	1 (0.9)	6 (2.8)	0.429
Previous treatment with ASA	10 (8.5)	36 (16.6)	0.042
Treatment with clopidogrel	114 (97.4)	208 (95.9)	0.458
Treatment with fibrinolytic (SK)	70 (59.8)	124 (57.1)	0.635
Treatment with unfractionated heparin	87 (74.4)	158 (72.8)	0.760
Treatment with enoxaparin	28 (23.9)	51 (23.5)	0.930
Treatment with ACEIs or ARBs	86 (73.5)	154 (71.0)	0.623
Treatment with beta blockers	106 (90.6)	189 (87.1)	0.342
Treatment with statins	110 (94.0)	210 (96.8)	0.259
Treatment with diuretics	15 (12.8)	31 (14.3)	0.711
Anterior or anterolateral STEMI	72 (61.5)	124 (57.1)	0.436
Lateral, inferolateral, or posterolateral STEMI	9 (7.7)	26 (12.0)	0.222
Inferior, inferolateral, inferoposterior, infero RV, or inferopostero RV STEMI	42 (35.9)	91 (41.9)	0.282
Age	55.98 ± 11.48	61.59 ± 13.41	<0.001
Systolic blood pressure (mmHg)	130.4 ± 28.3	127.4 ± 26.5	0.434
Diastolic blood pressure (mmHg)	79.0 ± 13.9	78.6 ± 13.7	0.950
Heart rate (beat/min)	78.9 ± 19.5	78.0 ± 21.0	0.519
Sum of ST deviation (mm)	15.62 ± 12.38	14.49 ± 9.55	0.765
Sum of ST elevation (mm)	12.28 ± 11.10	10.92 ± 9.02	0.892
Total cholesterol (mg/dl)	180.3 ± 42.5	176.1 ± 39.8	0.376
LDL cholesterol (mg/dl)	106.3 ± 31.8	100.1 ± 28.8	0.080
HDL cholesterol (mg/dl)	41.25 ± 9.98	41.26 ± 12.24	0.678
Triglyceride (mg/dl)	113.8 ± 56.5	128.1 ± 98.8	0.276
Fasting blood sugar (mg/dl)	120.1 ± 37.9	147.1 ± 76.7	0.032
Blood sugar at the admission time (mg/dl)	142.5 ± 58.0	183.1 ± 102.2	0.001
Blood urea nitrogen (mg/dl)	33.17 ± 10.40	40.21 ± 23.32	0.002
Creatinine (mg/dl)	0.98 ± 0.21	1.09 ± 0.39	0.032
Potassium (mmol/L)	4.21 ± 0.44	4.31 ± 0.56	0.061
Calcium (mg/dl)	9.16 ± 0.75	9.08 ± 0.85	0.596
Hemoglobin (g/dl)	13.70 ± 1.17	13.38 ± 2.43	0.053
Mean corpuscular volume (MCV) (mcm)	86.90 ± 5.47	86.08 ± 5.75	0.248
Alanine transaminase (ALT) (IU/L)	44.30 ± 55.77	48.02 ± 93.89	0.740
Aspartate transaminase (AST) (IU/L)	115.9 ± 141.3	127.9 ± 153.3	0.335
Alkaline phosphatase (ALP) (IU/L)	226.0 ± 68.1	224.7 ± 93.1	0.432
Erythrocyte sedimentation rate (ESR) (mm/h)	6.97 ± 8.97	10.18 ± 14.81	0.140
Uric acid (mg/dl)	5.61 ± 1.37	5.87 ± 1.64	0.173
Results of angiography and treatment options			
Angiography was not performed	19 (20.9)	41 (22.9)	

Minimal coronary occlusion, medical Tx	4 (4.4)	4 (2.2)	
PCI Tx	55 (60.4)	89 (49.7)	
CABG Tx	13 (14.3)	45 (25.1)	0.120

ACEIs: angiotensin converting enzyme inhibitors, ARBs: angiotensin receptor blockers, ASA: aspirin, CABG: coronary artery bypass graft surgery, CAD: coronary artery disease, CVA: cerebrovascular accident, HDL: high density lipoprotein, LDL: low density lipoprotein, PCI: percutaneous coronary intervention, SK: streptokinase, STEMI: ST elevation myocardial infarction, Tx: Treatment.

Table 2. Results of in-hospital outcomes, hospitalization, and ejection fraction before discharge in opium-addicted and non-addicted patients with ST elevation myocardial infarction

In-hospital results	Opium addicted n=117	Non-addicted n=217	*P* Value	RR	95% CI for RR
Composite end point	28 (23.9)	61 (28.1)	0.410	0.851	0.578-1.253
Death	5 (4.3)	12 (5.5)	0.618	0.773	0.279-2.140
Recurrent chest pain	21 (17.9)	38 (17.5)	0.920	1.025	0.632-1.662
Decompensated HF or PE	6 (5.1)	13 (6)	0.745	0.856	0.334-2.193

CI, confidence interval; HF, heart failure; PE, Pulmonary edema; RR, relative risk.

Table 3. Results of six-month follow up in opium-addicted and non-addicted patients with ST elevation myocardial infarction

In-hospital results	Opium addicted n=106	Non-addicted n=210	*P* Value	RR	95% CI for RR
Composite end point	44 (41.5)	97 (46.2)	0.429	0.899	0.687-1.176
Death	9 (8.5)	20 (9.5)	0.764	0.892	0.421-1.890
Recurrent chest pain	26 (24.5)	51 (24.3)	0.962	1.010	0.670-1.523
Recurrent STEMI	1 (0.9)	1 (0.5)	>0.999	1.981	0.125-31.363
Decompensated HF or PE	8 (7.5)	25 (11.9)	0.232	0.634	0.296-1.357

CI, confidence interval; HF, heart failure; PE, Pulmonary edema; RR, relative risk.

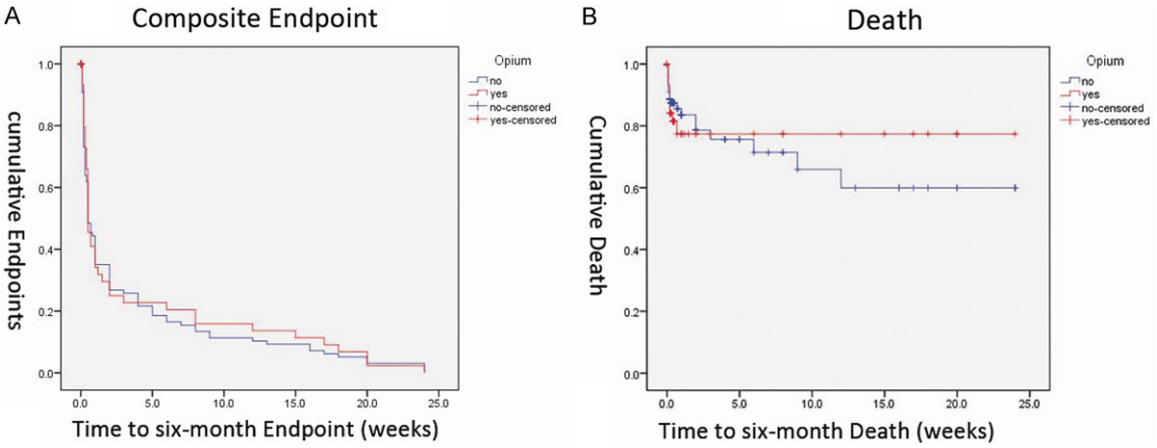

Figure 1. Kaplan-Meier curve of six-month composite endpoint (A) and death (B) of the opium-addicted and non-addicted groups. Caplan mayor of short term death and adverse outcome.

opium consumption and increased risk of death from ischemic heart diseases (hazard ratio: 1.90, 95% confidence interval: 1.57 to 2.29) [3]. Nevertheless, response to fibrinolytic therapy among opium-addicted patients has shown better response in some studies [15, 16].

The results of our study showed that in a group of initially medically treated patients with STEMI, in-hospital and short-term six-month outcomes were not significantly different in opium-addicted and non-addicted patients (**Tables 2** and **3**). Death, recurrent chest pain,

Table 4. Results of logistic regression analysis for possible confounders of in-hospital and six-month composite endpoints

In-hospital composite endpoint	Ex (B)	95% CI for Ex (B)	*P* value
Opium	0.929	0.501-1.725	.816
Sex (male)	1.452	0.787-2.678	.232
Age	1.004	0.985-1.024	.667
Cigarette smoking	1.194	0.628-2.268	.588
Hypertension	1.822	1.024-3.239	.041
Diabetes mellitus	2.002	1.053-3.805	.034
Hyperlipidemia	1.073	0.521-2.210	.848
Previous ASA intake	0.549	0.270-1.120	.099
6-month composite endpoint			
Opium	1.009	0.574-1.774	.974
Sex (male)	2.205	1.221-3.983	.009
Age	0.991	0.973-1.009	.325
Cigarette smoking	0.791	0.445-1.408	.426
Hypertension	1.365	0.814-2.288	.238
Diabetes mellitus	1.981	1.052-3.731	.034
Hyperlipidemia	1.126	0.573-2.213	.730
Previous ASA intake	0.505	0.257-0.992	.047

recurrent STEMI, decompensated heart failure, and pulmonary edema were also not significantly different among the two groups (**Tables 2** and **3**). Multivariate analysis confirmed that opium addiction was not an independent predictor of in-hospital or six-month composite adverse outcome. These findings are in accordance with some other studies about the in-hospital [7, 23-25] and six-month mortality [7] of opium addicted patients.

Although a single study of 98 deceased patients has shown less severe coronary artery disease in patients with positive blood levels for methadone or opium documented on autopsy specimens [26]. However, these patients are not a true representative of opium addiction. Furthermore, many other studies [1, 9, 10, 12, 13] except one [27] are in favor of some relationship between opium addiction and higher risk of coronary artery disease. Moreover opium consumption in any amount might be a reason for increase all-cause mortality and death due to ischemic heart disease [3].

The prevalence of opium addiction in our study was 34.8% which is more than that reported from the general population [1, 3, 5, 6]. The prevalence among patients with STEMI from different parts of Iran has been reported from a range of 9.9% [28] to 56.8% [29]. When we pulled the existing data from nine studies (a total of 4125 patients with STEMI), 24.5% were opium addicts. A comparison of STEMI patients with controls without STEMI from the other wards has shown a higher prevalence of opium addiction in one study [29] and a trend without statistical significance in the other [30]. Similar results have been reported in patients with IHD [8, 22, 27]. Furthermore, the prevalence of opium addiction has been reported to be higher in symptomatic MI than in silent MI [31]. Indeed, despite the higher prevalence of opium addiction in our patients with STEMI neither in-hospital nor 6-month outcomes were different in opium addicted patients.

High prevalence of addiction among patients with STEMI may be due to (1) underestimation of official records (2) or later opium abuse after the age of 40 [3, 32]. Coexistence of opium addiction with some other risk factors especially cigarette smoking were also common [3, 7, 8, 12, 16, 19, 20, 22-24]. The amount of opium consumption may also have an effect on the severity of atherosclerosis [1, 9, 13]. In a study on diabetic patients, there was a dose-response relationship between the dose of opium addiction and Gensini score found during angiography as a marker of extent of coronary artery disease [13]. However, the results of our study showed that higher opium consumption measured as servings/year did not have any effect on the in-hospital or six-month outcome.

Considering accidental intake of some other impure substances (polycyclic and heterocyclic aromatic hydrocarbons and primary aromatic amines) during opium abuse [33], might have an effect on the extent of coronary artery disease and risk factors [19]. In the present study, opium-addicted patients with STEMI were younger than non-addicted patients (mean age of the opium-addicted group was 55.98 ± 11.48 years in comparison to 61.59 ± 13.41 years, P<0.001, **Table 1**). Cigarette smoking has been almost universally shown to be more

prevalent in opium-addicted patients [3, 12, 13, 20] including STEMI patients [7, 16, 21, 23, 24] and patients undergoing CABG [8]. This has been proposed as one of the main reasons that opium addiction is a risk factor for more extensive coronary artery disease in some observational studies [9-12]. In our study, there was a significantly higher prevalence of cigarette smoking in the opium-addicted patients. However, using multivariate analysis adjusting for smoking did not change the results. Some opium addicts believe that opium decreases blood sugar [4] and for this reason they are accustomed to have higher sugar consumption. We found lower rate of diabetes mellitus in STEMI patients with opium addiction. Some other studies have shown similar results [8, 16, 20, 23] in patients with coronary artery disease while others could not confirm this finding [7, 21, 22, 24, 25, 34]. This observation may be related to a lower body mass index in opium consumers [8].

In the present study, there were also fewer patients with hypertension in the opium-addicted group. Although some studies have confirmed the same results [8, 21, 23] others have not [4, 7, 20, 22, 24, 25] needing future studies for definite answer.

Similar conflicting data exists about the effect of opium consumption on hyperlipidemia [4, 20-22, 24, 25] and plasma lipid profile [4, 7, 8, 16, 19, 34, 35]. Most of the studies have shown that the total cholesterol [7, 8, 13, 16, 19], LDL [7, 13, 16, 19, 35], HDL [7, 13, 16], and triglyceride [19, 35] have been similar in addicts and non-addicts patients. In our study, there was no significant differences seen in total cholesterol, LDL, HDL, and triglyceride levels between the groups.

The left ventricular ejection fraction was not significantly different in our patients with or without opium addiction (**Table 2**). This finding is in concordant with the fact that decompensated heart failure and pulmonary edema were not significantly different in our two patient groups (**Tables 2** and **3**). Many other studies have shown similar results regarding ejection fraction [7, 21, 24, 25], CCU admission period [24, 25], duration of hospitalization [25], prevalence of anterior STEMI [7, 21, 24, 25] and functional class [7, 24, 25].

Study limitation

Our study was conducted in those patients who had symptomatic STEMI. We cannot extrapolate our finding to patients with silent STEMI or those who did not seek medical attention. Opium might have an effect on the decision making warranting further investigation. Furthermore, our study was conducted in patients who were initially treated medically with streptokinase without availability of primary PCI.

The prevalence of opium addiction defined by an interview has limitation. Our sample size was relatively small with follow up of only 6 months. Larger sample size may further clarify the role of opium addiction in the natural history of STEMI. Opium addiction prevalence was as high as 34.8% in our patients with STEMI which appears to be far more than the general population. Moreover, our opium addicted patients were younger than non-addicts.

Conclusion

Our study revealed that opium addiction in patients presenting with STEMI initially treated with thrombolytic therapy did not have any effect on clinical outcome. Future larger studies are needed to definitely evaluate the effect of opium in patients with acute myocardial infarction.

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Disclosure of conflict of interest

None.

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