Original Article

Is the Urinary Morphine Concentration a Useful Marker for the Assessment of the Severity of Coronary Artery Stenosis in Opium Addicts?

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ABSTRACT

Background: Some studies have shown that opium is a potential risk factor for coronary artery disease (CAD). The method of opium use in most of these studies has been evaluated verbally. In the present study, we assessed the urinary morphine concentration to confirm opium addiction. This study aimed to evaluate the association between the urinary morphine concentration and the severity of coronary artery stenosis in opium addicts.

Methods: This study was conducted on 200 opium addicts admitted to the angiographic ward of a referral hospital at Kerman University of Medical Sciences. From these patients, 134 cases with CAD according to angiographic results were selected for our study. The patients were divided into 2 groups of mild CAD with < 50% stenosis and severe CAD with > 50% stenosis. Opium addiction and its severity were diagnosed based on the DSM IV criteria and confirmed by the measurement of the urinary morphine concentration.

Results: Severe coronary artery stenosis was detected in 77.6% of the opium addicts. A urinary morphine concentration exceeding the median index was associated with higher odds of severe CAD, but this association was not statistically significant (OR = 2.2, 95% CI: 0.62 to 7.9; $P = 0.21$).

Conclusions: The opium addicts in the current study were at a higher risk for severe CAD, but there was no significant relationship between the urinary morphine concentration and the severity of CAD. This paraclinical test was not an accurate marker for the assessment of the severity of CAD. The role of other alkaloids in opium should be evaluated. ***(Iranian Heart Journal 2019; 20(4): 64-70)***

KEYWORDS: Coronary artery disease, Opium addiction, Urinary morphine concentration, Angiography, Risk factors

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Received: January 24, 2019 **Accepted:** May 8, 2019

Opium addiction is a major problem in many countries, particularly in the Middle East. In Iran, the prevalence of opium addiction is estimated at over 3% in the general population. [1,2] In the Iranian province of Kerman, 5.3% of the general population and 22.5% of the rural population are addicted to opium. [3] A study in Kerman reported that the urine test of 15% of the subjects referred to one of the major medical diagnostic laboratories was positive. [4] Regular use of opium has been recognized as a risk factor for many diseases, including some cancers. [5-12] According to a previous study, the prevalence of opioid use was 20% in individuals with myocardial infarction and 10% in patients who underwent coronary artery bypass graft surgery. [3] Many people in Asia believe that opioids play a preventive or therapeutic role against hypertension, diabetes, hyperlipidemia, and cardiovascular diseases. [3] The adverse effects of opium on some cardiovascular risk factors have already been demonstrated. [13] The most common cause of death in opium addicts is CAD. [14] Marmor et al [15] found that opiate dependency was a protective factor for CAD (OR = 0.43, 95% CI: 0.2 to 0.94). Sadeghian et al [16] showed that opium consumption was a significant risk factor for CAD. Another study [17] revealed a relationship between opium and the outcome of myocardial infarction, while 2 other studies [18,19] showed no association between myocardial infarction and opium consumption.

Our literature review yielded a paucity of data on the effects of opium addiction on the severity of CAD. Accordingly, we sought to assess these effects by measuring the urinary morphine concentration.

METHODS

The present study, approved by the Ethics Committee of the Kerman Physiology Research Center, was performed on 200 opium-addicted patients admitted to the Angiographic Ward of Shafa Hospital, Kerman, between June 2011 and April 2012. From these cases, 134 patients who had CAD according to coronary angiography findings were selected.

Patients with valvular or congenital heart diseases, congestive heart failure; liver, kidney, or thyroid diseases; and those on medications that affected the urinary morphine concentration such as codeine were excluded. Opium addiction was defined based on the DSM IV criteria [20] and confirmed through the measurement of the quantitative level of morphine in urine (opiates kit 300/2000 Indianapolis). The urinary morphine concentration, as the index of the severity of addiction, was categorized to lower than the median (< 2623 ng/mL) and higher than the median (> 2623 ng/mL).

Demographic data, traditional cardiovascular risk factors, the daily dose of opium (g), and the duration and type of opium consumption were collected. Coronary angiography was performed via the Judkins method, [21] and all films were checked by an experienced cardiologist. According to the severity of coronary artery stenosis (based on the Gensini score), the patients were divided into 2 groups: mild CAD (< 50% luminal diameter stenosis in 1, 2, or 3 main coronary arteries) and severe CAD (> 50% luminal diameter stenosis in 1, 2, or 3 main coronary arteries).

Statistical Analysis

Relative and absolute frequencies, as well as the mean and the standard deviation, were used to present the statistics. The qualitative and quantitative variables were compared between the 2 groups of patients with mild and severe CAD using the χ^2 test and the Student *t*-test. The effects of the severity of opium addiction, measured according to the urinary morphine concentration, were evaluated using univariate and multivariate logistic regression models. All the data were analyzed with SPSS, version 20 (SPSS Inc, Chicago, IL, USA). A *P* value < 0.05 was considered statistically significant.

RESULTS

The present study recruited 134 opium addicts who had CAD. The mean age of the total population was 47 ± 9.15 years, and 75.4% of these patients were male. The mean duration of opium addiction was 13.2 ± 10. 5 months, and 45% the patients had addiction > 10 years. The median of the daily amount of opium used via both oral and smoking routes was 1.4 g/d. Additionally, 73% of the patients had a history of opium consumption by inhalation. The urinary morphine concentration was higher in the oral route than in inhalation, but this difference was not significant.

According to the coronary angiographic data, all the patients had CAD. Totally, 104 (77.6%) cases had severe CAD in 1, 2, or 3 main coronary arteries. Table 1 depicts the demographic characteristics in the 2 groups of mild and severe CAD. Only age and the daily dose of opium use were statistically significantly different between the mild and severe CAD groups (P = 0.040 and P = 0.039); the differences between the 2 groups concerning sex, obesity, family history of CAD, hypertension, hyperlipidemia, diabetes, and cigarette smoking failed to constitute statistical significance (P > 0.05). The urinary morphine concentration was higher in the patients with severe CAD (3342 ± 2115.5 ng/mL) than in those with mild CAD (2937.5 ± 2128.1 ng/ml); however, this difference was not significant (P = 0.36).

Table 1. Basic and clinical characteristics in the 2 groups of patients with mild and severe CAD

	Mild CAD	Severe CAD	*P* value
Gender			
male	23/30 (76.6%)*	78/104 (75%)	0.85
female	7/30(23.3%)	26/104(25%)	
DM	10/30 (33.3%)	26/103 (25.2%)	0.38
HTN	13/30 (43.3%)	46/104 (44.2%)	0.93
Hyperlipidemia	9/30 (30%)	42/104 (40.4%)	0.30
Age (>55 y)	9/30 (30%)	53/104 (51%)	0.04
Cigarette smoking			
never a smoker	13/30 (43.3%)	62/104 (59.6%)	
ex-smoker	9/30 (30%)	16/104 (15.4%)	0.15
current smoker	8/30 (26.7%)	26/104 (25%)	
Method of opium consumption			
oral	11/30 (36.7%)	24/100 (24%)	
vafour	16/30 (53.3%)	69/100 (69%)	0.28
sikh-sang	3/30 (10%)	7/100 (7%)	
Opium addiction duration			
<5 y	11/28 (39.3%)	27/98 (27.6%)	
5-10 y	6/28 (21.4%)	22/98 (22.4%)	0.46
>10 y	11/28 (39.3%)	49/98 (50%)	
Amount of opium usage (g/d)	1.63±1.8**	3.3±4.04	0.039
BMI (kg/m^2)			
normal (<25)	12/25 (48%)	39/68 (57.4%)	
overweight (25-29.9)	9/25 (36%)	22/68 (32.4%)	0.68
obese (≥30)	4/25 (16%)	7/68 (10.3%)	
Family history of CAD	6/30 (20%)	31/94 (33%)	0.17
Urinary morphine level (ng/mL)	2937.5±2128.1	3342±2115.5	0.36
Urinary morphine categories			
lower than median (<2623 ng/mL)	17/30 (56.7%)	50/103 (48.5%)	0.43
higher than median (>2623 ng/mL)	13/30 (43.3%)	53/103 (51.5%)	

* n/N (%) **mean±SD

DM, Diabetes mellitus; CAD, Coronary artery disease; BMI, Body mass index; HTN, Hypertension

According to the median index, the urinary morphine concentration was categorized to the higher than the median and lower than the median (Table 1). A urinary morphine concentration higher than the median (> 2623 ng/mL) was seen in 43.3% of the patients with mild CAD and 51.5% of the cases with severe CAD; this difference was not significant (*P* = 0.43).

Table2. Effects of different factors on the severity of CAD according to univariate and multivariate logistic regression analysis

Variable	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Urinary morphine level (>median)	1.38(0.61,3.1)	0.43	2.2(0.62,7.9)	0.21
Gender (male)	0.91(0.35,2.37)	0.85	1.31(0.23,7.5)	0.78
DM	0.67(0.28,1.62)	0.38	0.19(0.028,1.4)	0.10
HTN	1.037(0.45,2.35)	0.93	0.59(0.14,2.5)	0.47
Hyperlipidemia	1.58(0.66,3.7)	0.30	3.17(0.64,21.4)	0.14
Age (>55 y)	2.4(1.106,5.7)	0.046	6.2(1.4,26.4)	0.013
Cigarette smoking				
never a smoker	Ref	-	-	-
ex-smoker	1.97(0.80,4.8)	0.059	0.31(0.06,1.57)	0.15
current smoker	1.06(0.23,4.9)	0.44	0.43(0.09,2.03)	0.28
Method of opium consumption				
oral	Ref	-	-	-
vafour	1.97(0.80,4.8)	0.13	0.82(0.16,4.1)	0.81
sikh-sang	1.06(0.23,4.9)	0.93	1.75(0.18,16.3)	0.62
Opium addiction duration				
<5 y	Ref	-	-	-
5-10 y	1.49(0.47,4.6)	0.49	2.25(0.35,14.3)	0.39
>10 yr	1.81(0.63,4.7)	0.22	1.4(0.25,7.9)	0.68
Amount of opium usage (g/d)	1.23(1.13,1.52)	0.047	1.27(1.22,1.52)	0.01
BMI (kg/m^2)				
normal	ref	-	-	-
overweight	0.75(0.27,2.06)	0.53	0.30(0.068,1.33)	0.11
obese	0.53(0.13,2.1)	0.38	0.82(0.077,8.7)	0.89
Family history of CAD	1.96(0.72,5.3)	0.18	0.56(0.13,2.4)	0.45

DM, Diabetes mellitus; CAD, Coronary artery disease; BMI, Body mass index; HTN, Hypertension

DISCUSSION

The urinary morphine concentration in the opium addicts recruited in the present study had no significant correlation with the severity of CAD. However, after we made adjustments vis-à-vis the traditional cardiovascular risk factors, the logistic regression analysis showed that a higher urinary morphine concentration (> 2623 ng/mL) increased the risk of CAD (OR = 2.2) and that more than one-third of the addicts had severe CAD.

Masoumi et al [22] in 2009 and Davoodi et al [19] in 2006 assessed the relationship between opium addiction and the severity of CAD and showed that opium addiction had a higher risk for severe CAD, although the relationship was not statistically significant and was confounded by some cardiovascular risk factors. Opium addiction in both of those studies was diagnosed by patient self-report and not by paraclinical tests. This problem may have led to an underestimation of addiction and affected their results. Since most narcotics have a higher concentration in urine than in plasma, [20] we measured the urinary morphine concentration for a definite diagnosis of opium addiction and its severity. In any duration of addiction, the

urinary morphine concentration was higher in oral administration; nonetheless, the difference was statistically significant.

We observed no significant correlation between the urinary morphine concentration and the duration of addiction. After we made adjustments regarding the confounding factors, the daily dose of opium consumption had a higher risk for severe CAD. Additionally, the method and duration of addiction (> 5 y) had a higher risk for severe CAD, but this relationship was not significant.

These findings suggest that the effects of opium on CAD can be related to other alkaloids in opium or the method of consumption may influence the absorption of opium and the duration of action. It should be mentioned that many impurities are added during the processing of these drugs in Iran in order to gain a larger profit; some of these substances may have poisonous effects. Indeed, a previous investigation demonstrated that impurity—in terms of the level of lead—was high in the blood of the opium-addicted subjects; inorganic lead may have severe toxicity, carcinogenic effects, and even adverse effects on CAD. [23-25] Several epidemiological and clinical studies have found a causal relationship between chronic lead exposure and CAD. [26, 27]

Asgari et al [13] in 2008 assessed the effects of opium addiction on some cardiovascular risk factors and found that the blood morphine concentration was significantly higher in oral consumption and reported a direct correlation between this concentration and the duration of addiction. That study showed the deleterious effects of opium on some cardiovascular risk factors, with the method of sikh-sang having the worst effect. In our study, after we made adjustments concerning the confounding factors, the method of sikh-sang showed higher odds of severe CAD than did the other methods; nevertheless, this relationship was not statistically significant. [10] In contrast, Azimzadeh and colleagues [18] in 2005 showed no association between myocardial infarction and opium consumption.

The mechanisms of the association between opium and the incidence of CAD are not yet well understood. With the increasing evidence on the association between opium use and the incidence of CAD, more studies are needed to elucidate the mechanisms.

Smoking is one of the main risk factors for cardiovascular disease. [28,29] However, the association between smoking and the incidence of CAD was not statistically significant in our study. It is likely that the small sample size was responsible for this finding.

Limitations

We could not show an accurate relationship between some cardiovascular risk factors and the severity of CAD because of the small sample size and the absence of a control group due to the cost of opiates kits. Another drawback of note is the lack of data regarding the amount of morphine and other alkaloids in opium, which may have affected our results.

CONCLUSIONS

The findings of the current study indicated that opium addiction was correlated with higher odds of severe CAD, but the urinary morphine concentration was not an accurate index to assess this correlation.

Future studies should focus on other alkaloids in opium and assess their effects on CAD.

Conflict of Interest

The authors hereby declare that they have no conflicts of interest.

REFERENCES

1. National policy and strategies about prevention and control of addiction. 2005. Tehran, Iran : Headquarter against opiate abuse and smuggled.

2. Rahimimovaghar A : Guideline for prevention and treatment of addiction. Tehran prevention of vice cultural welfare organization, 1997

3. Ziaaddini H, ziaaddini MR. The household survey of drug abuse in kerman, Iran. J Applied sci : 2005 ; 5(2) : 380-2.

4. Nakhaee N, Divsalar K, Meimandi M, Dabiri S. Estimating the prevalence of opiates use by unlinked anonymous urine drug testing: a pilot study in Iran. Substance use & misuse. 2008; 43:513 – 520.

5. Nasrollahzadeh D, Kamangar F, Aghcheli K, Sotoudeh M, Islami F, Abnet CC, et al. Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. Brit J Cancer. 2008; 98:1857 – 1863.

6. Masjedi MR, Naghan PA, Taslimi S, Yousefifard M, Ebrahimi SM, Khosravi A, et al. Opium could be considered an independent risk factor for lung cancer: a case-control study. Respiration. 2013;85(2):112-8.

7. Sadjadi A, Derakhshan MH, Yazdanbod A, Boreiri M, Parsaeian M, Babaei M, et al. Neglected role of hookah and opium in gastric carcinogenesis: A cohort study on risk factors and attributable fractions. International Journal of Cancer. 2014;134(1):181-8.

8. Naghibzadeh-Tahami A KN, Yazdi-FeyzabadiV,Varzandeh M, Haghdoost AA. Opium as a risk factor for upper gastrointestinal cancers: a population-based case-control study in Iran. Archives of Iranian medicine. 2014;17(1):2.

9. Akbari M, Naghibzadeh-Tahami A, Khanjani N, Baneshi MR, Kamali E, Hesampour M, et al.Opium as a Risk Factor for Bladder Cancer: A Population-based Case-control Study in Iran. Archives of Iranian medicine. 2015;18(9):567.

10. Naghibzadeh-Tahami A, Feyzabadi VY, Khanjani N, Ashrafi-Asgarabad A ,Alizaeh H, Borhaninejad VR, Moradi-Joo M, Zeinali M, Zahedi MJ ,Aghaee-Afshar M, Haghdoost AA. Can opium use contribute to a higher risk of colorectal cancers? A matched case-control study in Iran. Iranian journal of public health. 2016 Oct;45(10):1322 .

11. Lankarani KB, Khosravizadegan Z, Naghibzadeh-Tahami A, Akbari M ,Khodadost M, Honarvar B, Khodadost B, Goodarzi F, Jokari K, Sekhavati E ,Tabrizi R. Opium use and risk of lower gastrointestinal cancers : Population-based case-control study in South of Iran. International Journal of Cancer Management. 2017;10(6).

12. Hadji M, Marzban M, Gholipour M, Rashidian H, Naghibzadeh-Tahami A ,Haghdoost AA, Rezaianzadeh A, Rahimi-Movaghar A, Moradi A, Seyyedsalehi M, Poustchi H. National Study of Opium and Cancer in Iran (IROPICAN :) Study Protocol and Results of the Pilot Phase .

13. Asgari S, Nisal sarrafzadegan, Gholam-Ali naderi. Effect of opium addiction on new and traditional cardiovascular risk factors. Lipids in health and disease. 2008 ; 7 : 42.

14. Bjornaas MA, Bekken AS, Ojlert A, Haldorsen T. A 20-year prospective study of mortality and cause of death among hospitalized opiod addicts in oslo. BMC psychiatry 2008 ; 8. 8

15. Marmor M, Penh A, Widmer K, Ievin RI. coronary artery disease and opioid use. Am j cardiol 2004 ; 93(10) : 1295-1297

16. Sadeghian S, Darvish S, Davoodi G, Salarifar M, Mahmoodian M, Fallah N, et al. The association of opium with coronary artery disease. European Journal of Cardiovascular Prevention & Rehabilitation. 2007;14(5):715-7.

17. Sadr Bafghi SM, Rahei M, Bahadorzadeh L, Namayeh SM. Is opium addiction a risk factor for acute myocardial infarction?. Acta medica Iranica 2005 ; 43(3) : 218-22.

18. Mann DL, Zipes DP, Libby P, Bonow RO. Braunwald's heart disease e-book: a textbook of cardiovascular medicine 10th ed. Elsevier Health Sciences; 2014.

19. Davoodi G, Sadeghian S, Akhondzadeh S, darvish S. A comparison of specifications, short-term prognosis of acute myocardial infarction in opium dependent patients and non dependents. German j psychiatry 2005 ; 8 : 33-37.

20. American psychiatric association. Diagnostic and statistical manual of mental disorders DSM-

IV-TR 4th ed. Washington DC : american psychiatric publishing ; 2000

21. Mann DL, Zipes DP, Libby P, Bonow RO. Braunwald's heart disease: a textbook of cardiovascular medicine: Elsevier Health Sciences; 2014.

22. Masoumi M, Shahesmaeili A, Mirzazadeh A, Tavakoli M. opium addiction and severity of coronary artery disease : a case-control study. Journal research of medical sciences 2010 ; 15(1) : 27-32

23. Aghaee-Afshar M, Khazaeli P, Behnam B, Zadehkermani M, Ashraf-Ganjooei N. Presence of Lead in Opium. Arch Iranian Med.2008; 11(5):553 – 554.

24. Salehi H, Sayadi A, Tashakori M, Yazdandoost R, Soltanpoor N, Sadeghi H, et al. Comparison of serum lead level in oral opium addicts with healthy control group. Arch Iranian Med.2009; 12(6):555 – 558.

25. Amiri M, Amini R. A comparison of blood-lead level (BLL) in opi-um-dependant addicts with healthy control group using the graphite furnace/atomic absorption spectroscopy (GF-AAS) followed by chemometric analysis.Iran Red Crescent Med J. 2012; 14(8):488 – 491.

26. Navas-Acien A, Guallar E, Silbergeld EK, Rothenberg SJ. Lead exposure and cardiovascular disease: a systematic review. Environmental health perspectives. 2007:472-82.

27. Vaziri N, Gonick H. Cardiovascular effects of lead exposure. Indian Journal of Medical Research. 2008;128(4):426.

28. Pyrgakis VN. Smoking and cardiovascular disease. Hellenic J Cardiol. 2009;50(3):231-4.

29. Chen Z, Boreham J, editors. Smoking and cardiovascular disease. Seminars in vascular medicine; 2002.