

## Cerebrovascular Reactivity and Carotid Intima-Media Thickness in Opium Dependents: A Case-Control Study

Akbar Hamzиеe-Moghadam MD<sup>1</sup>, Farhad Iranmanesh MD<sup>1</sup>,  
Ali Arabpour-Fathabadi MD<sup>2</sup>, Forugh Mohammadi MD<sup>2</sup>

### Original Article

#### Abstract

**Background:** There is still no consensus among researchers on the impact of opium dependency on cerebrovascular stenosis. Some studies suggest that opium may be a risk factor for ischemic stroke. This study compared carotid intima-media thickness (CIMT) and cerebrovascular reactivity between opium-dependent and healthy people.

**Methods:** This case-control study was done among opium addicts at Shafa hospital in Kerman, Iran, in year 2018. People with systemic disease or who took any medicine were excluded from our study. The control group were selected from healthy non-addicted volunteers. The control group was matched in age and sex with the case group. Cerebrovascular reactivity of middle cranial artery and intima-media thickness of carotid artery were measured for all in both groups. The results were analyzed using chi-square, independent samples t, and logistic regression tests.

**Findings:** 47 opium addicts and 47 healthy people entered this study. 88% of them were men and 12% were women. 68.1% of the case group and 31.9% of the control group were cigarette smokers; this difference was statistically significant. Comparison of cerebrovascular reactivity and CIMT between the two groups was statistically significant ( $P < 0.001$ ). This relationship remained significant for the CIMT after removing confounding factors ( $P = 0.018$ ).

**Conclusion:** Overall, our findings show that opium dependency affects the carotid intima-media thickness as an indicator of cerebral atherosclerosis.

**Keywords:** Opium; Intima-media thickness; Cerebrovascular diseases; Stroke; Transcranial Doppler sonography

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1- Professor, Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran

2- Neurologist, Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran

Correspondence to: Ali Arabpour-Fathabadi MD, Email: [dr.arabpour@outlook.com](mailto:dr.arabpour@outlook.com)

## Introduction

Ischemic stroke is one of the most common neurological disorders due to a high prevalence of vascular atherosclerosis risk factors among people.<sup>1</sup> The most common causes of ischemic stroke include large vessels atherosclerosis, cardiac embolism, and small vessels disease. Up to now, hypertension, hyperlipidemia, diabetes mellitus, and cigarette smoking have been known as risk factors for atherosclerosis.<sup>1-4</sup>

In recent years, opium addiction has been studied as one of the possible causes of atherosclerosis, and its impact on myocardial infarction (MI) has been illustrated in some studies.<sup>5</sup> Previous studies showed a high prevalence of opium dependency in patients with ischemic stroke;<sup>6</sup> but the pattern of vascular stenosis of them did not differ from the control group.<sup>7</sup> In another study, oral usage of opium known to be a protective factor for ischemic stroke.<sup>8</sup>

B-Mode Doppler sonography can be used to study the process of atherosclerosis in cerebrovascular arteries. Abnormal results of carotid intima-media thickness (CIMT) are one of the most important predictors of vascular events.<sup>9</sup> Cerebrovascular reactivity is another indicator of asymptomatic carotid artery stenosis<sup>10-12</sup> that is measured by examination of intracranial blood flow changes by a vasodilatory stimulus such as CO<sub>2</sub>.<sup>11</sup> It can also predict ischemic events in carotid stenosis.<sup>13-15</sup>

Due to high prevalence of opium addiction in some countries, and lack of consensus on the role of opium in ischemic diseases, our study tried to compare CIMT and cerebrovascular reactivity between opium addicts and the control group.

## Methods

This case-control study was done among opium addicts at Shafa hospital in Kerman, Iran, in year 2018. The inclusion criteria for the case group was all people over 30 years old who were opium dependents according to the 10<sup>th</sup> version of the International Statistical Classification of Diseases and Related Health Problems (ICD10). Individuals with any systemic disease such as diabetes mellitus, respiratory disorder, rheumatoid or any other inflammatory disease, pregnancy, and taking any medicine or oral contraceptive pill (OCP) were excluded from our

study. These people were selected from Addiction Treatment Centers in Kerman City (before treatment started). They were addicted to "opium only" or "opium and cigarette". Since cigarette smoking is often an accompaniment to opium addiction in society, we measured and recorded the amount of smoking as a confounding factor in both case and control groups.

For all cases, ultrasonography was performed with a Multi-Dop X Digital-DWL ultrasound instrument, and cerebrovascular reactivity and CIMT were calculated. IMT at the far wall of common carotid artery was measured and recorded.<sup>16</sup> Cerebrovascular reactivity was determined by apnea test. In this test, a 2.5-Hz probe was fixed on temporal window, and focused on middle cerebral artery at a depth of 5 cm until the maximum flow was detected; and then, the middle cerebral arterial (MCA) flow was recorded continuously. After recording of mean flow velocity (MFV) in a 4-second period, the patient was asked to have a normal breath, and then hold it for 30 seconds (without Valsalva maneuver). At the end of this period, MFV was recorded again. After a rest for 3 minutes, the patient was asked to breathe fast for one minute, and MFV was recorded. Finally, reactivity was calculated by the following formula:<sup>17</sup>

$$\text{MCA Reactivity} = \frac{\text{MFV}_{\text{Apnea}} - \text{MFV}_{\text{Hyperventilation}}}{\text{MFV}_{\text{Rest}}} \times 100$$

The control group were selected from healthy non-addicted volunteers, and matched in age and sex with the case group. The sample size of 47 people was estimated within each group ( $P < 0.050$ , and statistical power of 80%).

This study was approved by the Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran. All results were analyzed using chi-square, independent samples t, and logistic regression tests via SPSS software (version 22, IBM Corporation, Armonk, NY, USA).  $P < 0.050$  was the statistical significance level.

## Results

The opium-dependent group included 43 men (91.5%) and 4 women (8.5%). 40 men (85.1%) and 7 women (14.9%) were admitted to the healthy control group. These two groups did not differ significantly in gender ( $P = 0.336$ ). The mean age was not significantly different between the two groups ( $P = 0.520$ ) (Table 1).

**Table 1.** The comparison of dependent variables between the groups

Variable	Group		P*
	Opium addict (mean ± SD)	Control (mean ± SD)	
Age (year)	47.87 ± 1.18	49.04 ± 1.37	0.520
Cigarette usage (pack-year)	8.06 ± 1.25	2.74 ± 0.95	0.010
CIMT (mm)	0.84 ± 0.03	0.62 ± 0.02	< 0.001
MCA reactivity (%)	64.82 ± 1.44	74.04 ± 1.42	< 0.001

SD: Standard deviation; CIMT: Carotid intima-media thickness; MCA: Middle cerebral arterial

\*Independent samples t test

32 cases in opium-dependent group (68.21%) and 15 (31.9%) in the control group were cigarette smokers, and this difference was significant between two groups ( $P < 0.001$ ). Besides, the cigarette pack-year index was significantly higher in opium users compared to control group ( $P = 0.010$ ) (Table 1).

In preliminary analysis by independent samples t test, the mean CIMT in opium-dependent group was significantly higher than control group, too ( $P < 0.001$ ) (Table 1).

The mean percentage of MCA reactivity was also significantly less in opium-dependent group ( $P < 0.001$ ) (Table 2).

After using logistic regression to eliminate the effect of cigarette as a confounding factor, the difference between CIMT in studied groups remained significant ( $P = 0.018$ ). However, this did not happen for the reactivity ( $P = 0.507$ ) (Table 2).

## Discussion

This study was conducted to evaluate the effect of opium addiction on cerebrovascular ultrasonography tests. Our study illustrates that opium addiction is associated with an increase in IMT of carotid arteries. This finding remained significant even after the removal of confounding factors such as cigarette smoking. Our findings indicate an increased risk of atherosclerosis in opium addicts.

In previous studies, the high value of this test was confirmed for detection of atherosclerosis and prediction of ischemic events. It also associated with presence of brain white matter lesions, left ventricular hypertrophy, and kidney

diseases.<sup>9,10,16,18</sup> Lorenz et al. reported that for an absolute CIMT difference of 0.1 mm, the future risk of MI increases by 10-15 percent, and the stroke risk increases by 13-18 percent.<sup>19</sup> Another study by O'Leary and Bots showed that IMT of internal carotid artery was more associated with MI and common carotid artery ischemic stroke.<sup>16</sup> Moreover, Saadatnia et al. compared CIMT in a group of 20 opium users and control group. In their study, CIMT was higher in opium-addicted group, but there was no significant relationship after removal of confounding factors such as cigarette smoking. As a result, further investigations with larger sample sizes were proposed.<sup>20</sup>

Although no more similar studies were found to allow us to compare our results with them, the following studies are noteworthy. In a study by Hamzei-Moghaddam et al., 105 patients with ischemic stroke and healthy control group were compared. The opium dependency was significantly higher in patients with stroke.<sup>21</sup> They also found in another study that, despite the higher prevalence of opium addiction in patients with ischemic stroke, the pattern of their stenosis did not differ with other non-addict patients.<sup>7</sup> From 2005 to 2013, five studies have been conducted on the association of opioid addiction and ischemic heart disease in Iran. All of them showed that opium addiction had a significant relationship with the incidence of ischemic heart disease.<sup>5,22-25</sup>

The second vascular examination technique we used was the determination of cerebrovascular reactivity by transcranial Doppler ultrasonography.

**Table 2.** The results of logistic regression test for variables

Variable	Crude			Adjusted		
	OR	P	CI	OR	P	CI
CIMT	0.004	< 0.001	0-0.06	0.004	0.018	0-0.39
MCA reactivity	0.10	< 0.001	1.04-1.15	1.03	0.507	0.94-1.13

OR: Odds ratio; CI: Confidence interval; CIMT: Carotid intima-media thickness; MCA: Middle cerebral arterial

Although we did not see any significant differences between two groups after eliminating the confounding factors, but the impact of atherosclerosis risk factors such as hypertension, cigarette smoking, and diabetes mellitus on cerebrovascular reactivity has been confirmed in previous studies.<sup>26-29</sup> It can also be used as a predictor of ischemic events in carotid stenosis.<sup>11-13,30</sup>

Acquiring history of underlying illnesses from individuals, and the absence of internal and cardiac examinations were the main limitations in our study, which we propose to consider in subsequent studies.

### Conclusion

In conclusion, our findings show that opium

dependency affects the CIMT as an indicator of atherosclerosis. The high prevalence of opium addiction in the Middle East,<sup>31</sup> and its impact on increasing mortality,<sup>32</sup> indicates the importance of this issue. So, the role of opium in the atherosclerosis process as a risk factor of vascular events should be taken into account.

### Conflict of Interests

The Authors have no conflict of interest.

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# واکنش‌پذیری عروق مغزی و ضخامت اینتیمای شریان کاروتید در افراد معتاد به تریاک: یک مطالعه مورد-شاهدی

دکتر اکبر حمزه‌ای مقدم<sup>۱</sup>، دکتر فرهاد ایرانمنش<sup>۱</sup>، دکتر علی عرب‌پور فتح‌آبادی<sup>۲</sup>، دکتر فروغ محمدی<sup>۲</sup>

## مقاله پژوهشی

## چکیده

**مقدمه:** هنوز در مورد تأثیر مصرف تریاک بر تنگی عروق مغزی، در میان محققان اتفاق نظر وجود ندارد. برخی از مطالعات نشان می‌دهد که تریاک ممکن است عامل خطر برای بروز سکته مغزی باشد. هدف از انجام پژوهش حاضر، مقایسه ضخامت اینتیمای شریان کاروتید و واکنش‌پذیری عروق مغزی در معتادان به تریاک و افراد سالم بود.

**روش‌ها:** این مطالعه به صورت مورد-شاهدی بر روی افراد معتاد به تریاک در بیمارستان شفای کرمان در سال ۱۳۹۷ انجام گردید. افرادی که بیماری‌های سیستمیک و یا سابقه مصرف هرگونه دارو داشتند، از مطالعه حذف شدند. نمونه‌های گروه شاهد از افراد داوطلب سالم غیر معتاد به تریاک انتخاب و از نظر سنی و جنسی با گروه مورد همسان‌سازی شدند. واکنش‌پذیری شریان مغزی میانی و ضخامت اینتیمای شریان کاروتید مشترک، در بیماران هر دو گروه محاسبه گردید. داده‌ها با استفاده از آزمون‌های  $\chi^2$  و Independent t و Logistic regression مورد تجزیه و تحلیل قرار گرفت.

**یافته‌ها:** ۴۷ فرد معتاد به تریاک و ۴۷ فرد سالم در تحقیق شرکت نمودند. ۸۸ درصد از نمونه‌ها مرد و ۱۲ درصد زن بودند. ۶۸/۰۰ درصد از افراد گروه مورد و ۴/۲۳ درصد از افراد گروه شاهد سیگار مصرف می‌کردند که این تفاوت از نظر آماری معنی‌دار بود. اختلاف معنی‌داری در ضخامت اینتیمای شریان کاروتید و واکنش‌پذیری در شریان مغزی میانی بین دو گروه وجود داشت ( $P < ۰/۰۰۱$ ) که این ارتباط پس از حذف عوامل مخدوشگر، در مورد ضخامت اینتیمای شریان کاروتید معنی‌دار باقی ماند ( $P = ۰/۰۱۸$ ).

**نتیجه‌گیری:** بر اساس نتایج به دست آمده از مطالعه حاضر، اعتیاد به تریاک بر ضخامت اینتیمای شریان کاروتید مشترک، به عنوان شاخصی از روند آترواسکلروزیس، تأثیرگذار می‌باشد.

**واژگان کلیدی:** تریاک، ضخامت اینتیمای شریان مغزی، سکته مغزی، سونوگرافی داپلر ترانس کرانیال

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Email: [dr.arabpour@outlook.com](mailto:dr.arabpour@outlook.com)

۱- استاد، مرکز تحقیقات بیماری‌های مغز و اعصاب، دانشگاه علوم پزشکی کرمان، کرمان، ایران  
۲- نورولوژیست، مرکز تحقیقات بیماری‌های مغز و اعصاب، دانشگاه علوم پزشکی کرمان، کرمان، ایران  
نویسنده مسؤول: دکتر علی عرب‌پور فتح‌آبادی