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Original Article

Opium Consumption and Myocardial Infarction in Osteoarthritis Patients: A Propensity Score Matched Cohort Study

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Abstract

Introduction: In recent years, the use of drugs with opioid compounds in patients with osteoarthritis has attracted increasing attention. However, long-term use of these drugs may cause severe side effects, including cardiovascular diseases. The present study aimed to investigate the relationship between the use of opium substances and myocardial infarction in osteoarthritis patients using a propensity score matching (PSM) approach.

Methods: We designed this study as a retrospective cohort study. The data were collected from 2016 to 2020. We identified confounding variables using the modified disjunctive cause criterion method. We matched individuals exposed to opium (opium users) and those unexposed to opium (non-users) by propensity score. We examined the distributions of opium users and non-users, both with and without propensity score matching. To determine the relationship between exposure to opium and heart attack in osteoarthritis patients, the Cox regression method was used.

Founding: The participants' mean age was 49.85 ± 9.61 years, with 32.3% being men and 67.7% being women. We excluded individuals with cardiovascular disease from the baseline examination. Before PSM, the incidence rate in the total study sample was 2.96 per 1000 person-years. The relationship between opium consumption and heart attack was inverse before matching (hazard ratio, HR 0.73, 95% confidence interval (95% CI 0.58-0.98). After matching, the HR showed an increase of 24% (HR 1.24, 95% CI 0.87-1.76)

Conclusion: The findings of the present study suggest that opioid consumption is associated with an increased risk of heart attacks in osteoarthritis patients. Confirmation of this finding in future studies would indicate the need for monitoring these patients with a view towards primary prevention of modifiable cardiovascular risk factors.

Keywords: Opium addiction, Myocardial infarctions, Osteoarthritis, Propensity scores

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Introduction

Osteoarthritis is considered to be the most common joint disease worldwide that is associated with inflammation and chronic pain.[1,2] In 1990, there were 247.57 million cases worldwide, which increased to 527.81 million in 2019. Also, in 2019, this disease was the 15th cause of years of life lived with disability (YLDs) in the world.[3,4] Most cases of this disease occur in middle-aged and elderly.[5] Age is a significant risk factor for this disease.

Osteoarthritis significantly reduces the quality of life for sufferers. Osteoarthritis therapeutic strategies include controlling pain and inflammation. For this purpose, anti-inflammatory drugs such as NSAIDs, opioids, and hydroxychloroquine, are used. However, in addition to gastrointestinal side effects, these drugs may increase the risk of cardiovascular diseases. [6-10]

Several studies indicated that different doses of non-steroidal drugs, including ibuprofen, naproxen, rofecoxib, and celecoxib, may be risk factors for myocardial infarction.[11-14] For this reason, in recent years, opioid compounds have attracted attention as an alternative to non-steroidal medication for pain control, as it is believed that these drugs have fewer side effects than non-steroidal drugs.[15,16]

Opioid consumption, however, may result in drug addiction.[17] In addition, opioids may also be related to cardiovascular diseases, especially myocardial infarction.[18] Although some of these studies failed to control for confounding, some used logistic regression and reported adjusted results that confirmed the presence of an association between opioids and myocardial infarction. [19-23] One of the methods that can more effectively control for confounding effects is propensity score matching, a method that was first proposed by Rubin and Rosenbaum.[24] The present study aimed to investigate the relationship between opium substances and heart attack in osteoarthritis patients using propensity score matching (PSM).

Methods

Study Design and Data Source

In this retrospective cohort study, the information were collected from the Fasa Adults Cohort Study (FACS), which is an initiative of the Ministry of Health of Iran. The data in this manuscript cover the years 2016 to 2020. The total cohort numbered 10,131 people. In this study, 4,266 individuals with confirmed osteoarthritis symptoms, as determined by a physician specialist, were included.[25] Raw data were received under the full supervision of FASA cohort investigators after receiving the proposal's Ethical approval code from the Research Committee of Kurdistan University of Medical Sciences (Ethical approval code: IR.MUK.REC1399.285).

Clinical Characteristics

The individuals included in the study were ≥ 35 years old. We evaluated the physical and clinical conditions of each selected person in each of the periods. In each period, demographic information and lifestyle; family history of chronic diseases; history of chronic diseases; and a list of consumed drugs were collected through a questionnaire. The trained staff measured weight, height, and blood pressure levels. Also, fasting blood sugar and blood cholesterol levels were performed. Body mass index was calculated by dividing weight in kilograms by the square of height. All data were collected using traditional approaches.[26]

Study Sample

Patients aged 35–70 years with osteoarthritis symptoms were included from 2016 to 2020 (phase 4 of the parent cohort). Exclusion criteria were an incomplete medical record, body mass index of less than 15 kg/m^2 or more than 35 kg/m^2. Based on a vast literature, individuals with class 2 obesity have a high risk of developing hypertension and osteoporosis. It is also an independent risk factor for heart attacks and strokes. Individuals with a BMI lower than 15 have musculoskeletal problems that are directly related to osteoarthritis[27-30], and lack of information on opium exposure. After removing ineligible individuals from the study, 4266 patients remained, which formed the study base from which propensity score matched pairs were selected (Figure 1).

Outcome

The definition of myocardial infarction was based on ICD-10 and confirmed by the physician in each of the five annual examinations.[31] According to the Persian Cohort guidelines, individuals are diagnosed with myocardial infarction if they exhibit typical clinical symptoms (chest pain), abnormal electrocardiography, and elevated troponin levels.

Exposure of Interest and Covariates

The exposure of interest was opium abuse. Based on the Persian Cohort guideline and questionnaire, individuals exposed to opium use are defined as traditional users. Opium abuse was defined as consumption of at least once a week during the previous six months.[25] Covariates included age, sex, race, educational level, marital status, family history of chronic disease, diabetes, blood pressure levels, use of steroid drugs, body mass index, blood cholesterol, smoking, and alcohol consumption.

Propensity Score Matching

The propensity score is defined as the conditional probability of receiving a particular treatment or exposure given a set of observed covariates considered as potential confounders. The most common approach to estimate the PS is logistic regression, where confounding variables are included as covariates in the model. There are four primary approaches to utilize propensity scores: stratification, matching, regression adjustment, and weighting. Matching is frequently applied in studies where the number of unexposed individuals substantially exceeds that of exposed individuals, and it has been the most commonly used approach in epidemiological research. PSM is considered the most practical, particularly in cohort studies when the exposure is relatively rare. Common PSM algorithms include stratification matching, nearest neighbor matching, N:N matching, radius matching, kernel matching, Mahalanobis matching, and caliper matching. In some studies, hybrid methods combining two algorithms have been employed. Nevertheless, evidence suggests that nearest neighbor matching is the most frequently used algorithm, as it minimizes sample loss compared with other methods. Individuals with similar scores typically within a range of 0.1 to 0.5 are matched and calibrated. After calibrating and matching individuals, the next step is to calculate the average treatment effect (ATT) of the propensity scores in the exposed group and subtract it from the corresponding average in the non-exposed group.[24,32-34]

Statistical Analyses

The Shapiro-Wilk test was used to assess the normality of the data. After using the normality test, the central limit theorem was used for assessing high-volume data. The modified disjunctive cause criterion method was used to select confounding variables. The t-test was used for continuous data, the Chi-square test was used for categorical data, and non-parametric tests were utilized

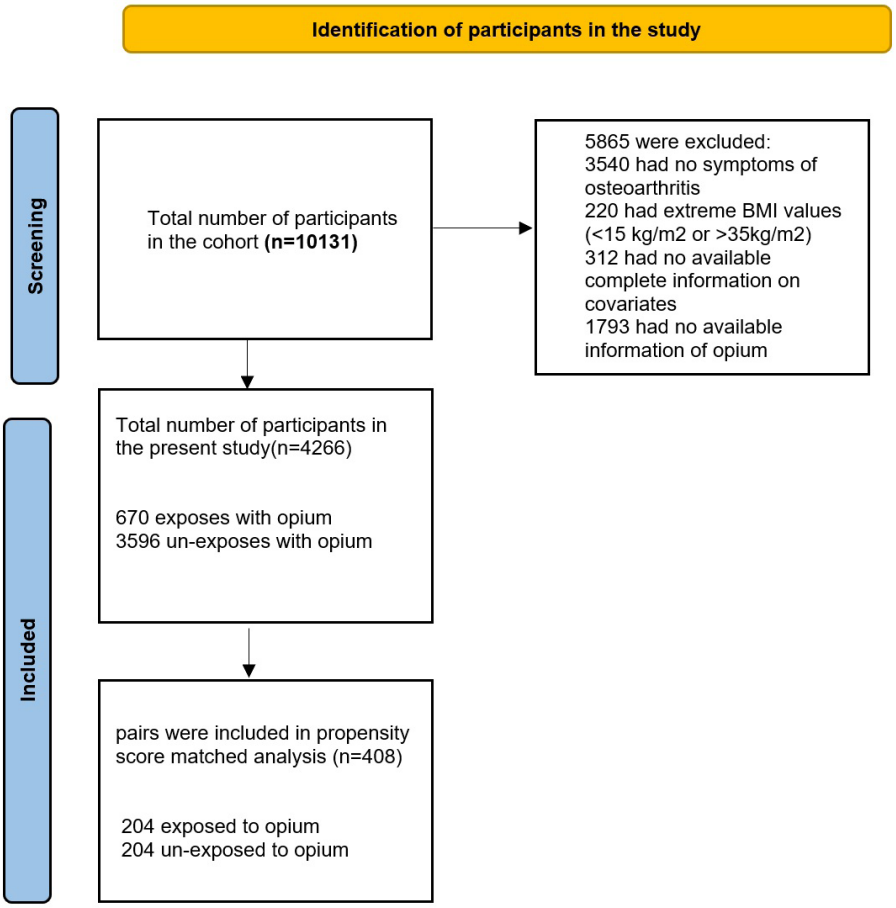

Figure 1. PRISMA diagram

for non-normal data.

Three analytic approaches were used in the analysis: (1) propensity score with individual matching, which yielded 204 pairs of exposed vs. unexposed individuals; (2) calculation of cumulative incidence ratios – based on the Kaplan-Meier survival approach; (3) calculation of incidence rate ratios based on yearly averages (ratio of rates per 1,000 person-years at risk); and (4) conduct of multivariable adjustment using Cox regression. These measures of association were reported before and after PSM. The results from strategies 2-4 were based on the total study base (n = 4266).

The propensity score (PS) for each individual was based on exposure to opium and confounding covariates. Two hundred and four individuals who did not report opium consumption were matched to the nearest individuals in the study base roster reporting opium consumption with the same characteristic in a one-to-one manner. After this step, the average treatment effect (ATT) method was used to calculate the mean difference in treatment based on the scores obtained.[35] After obtaining two matched groups, Chi-square and t-test values were calculated for the data based on the data type. These calculations were performed to obtain the p-value between confounding variables and exposure and to compare these relationships with the non-matched case.

For the whole sample, rate, rate ratios, and hazard ratios were calculated. Cox regression was used for multivariable adjustment of hazard ratios expressing the association between opium exposure and myocardial infarction. All analyses were performed using Stata.

Results

Four thousand two hundred and twenty-six participants comprised the analytic study population. 32.30% of the participants were men and 67.70% were women with the mean age of 49.85 ± 9.61 years (Table 1). There were 670 people exposed to opium consumption (15.71%). As shown in Table 1, the main covariates had significant relationships with the exposure ($P < 0.05$).

Propensity score matching yielded 204 pairs according to the exposure. As shown in Table 1, both for matched groups and for the full unadjusted study base, there were no significant relationships between covariates and exposure.

The cumulative incidence and incidence rates per 1000 person-years and their ratios with and without PSM are presented in Table 2. In the entire study base, the unadjusted incidence rate of myocardial infarction without PSM was 3.83 per 1000 person-years. In the opium-exposed group, this rate was 2.96 per 1000 person-years; while in the unexposed group, it was 3.99 per 1000 person-years. The cumulative incidence for the whole study base was 2.01 (95% confidence interval (CI): 0.6, 2.68); in those exposed and not exposed to opium, cumulative incidences were 1.92 and 2.76, respectively (Table 2).

Table 1. Baseline characteristics without and with propensity score matching

Characteristics	Whole study base			With propensity score matching		
	Exposed to opium	Un-exposed to opium	*P*-value	Exposed to opium	Un-exposed to opium	*P*-value
Participants	670	3596		204	204	
Age (years)	48.34±9.0	50.13±9.6	<0.001	49.16±8.9	50.61±10.1	0.12*
Gender			<0.001			1.00#
Female (%)	663 (94.4)	745 (20.7)		169 (82.8)	169 (82.8)	
Race/ethnicity (%)						
Persian	345 (51.4)	1799 (50.0)	0.6	105 (51.4)	102 (50.0)	0.76#
Turkish	194 (28.9)	1215 (33.7)	0.01	53 (25.9)	57 (27.9)	0.65
Arab	52 (7.7)	210 (5.8)	0.05	17 (7.8)	15 (7.3)	0.71
Other races	79 (11.7)	372 (10.3)	0.24	29 (14.7)	30 (14.7)	0.88
BMI(kg/m^2) (mean)	26.23±4.9	26.28±5.0	0.83	26.140±4.5	26.140±4.5	0.24#
place of residence (%)			0.24			0.49#
Urban	138 (20.6)	611 (16.9)		35 (17.1)	30 (14.7)	
Village	532 (79.4)	2985 (83.0)		169 (82.8)	174 (85.2)	
Marital status (%)						
Single	13 (1.9)	171 (4.7)	0.03	2 (0.9)	3 (1.4)	0.65#
Married	649 (96.8)	3050 (84.8)	<0.001	194 (95.1)	194 (95.1)	1.00
Divorced	8 (1.19)	375 (10.43)	<0.001	8 (3.92)	7 (3.43)	0.79
Education (%)						
Illiterate	235 (35.0)	1955 (54.3)	<0.001	89 (43.6)	90 (44.1)	0.92#
Elementary	222 (33.1)	1113 (30.9)	0.26	73 (35.7)	66 (32.3)	0.46
Guidance	153 (22.8)	324 (9.0)	<0.001	25 (12.2)	32 (15.6)	0.31
High	47 (7.01)	147 (4.09)	0.001	13 (6.37)	11 (5.39)	0.67
Undergraduate	4 (0.6)	13 (0.3)	0.37	2 (0.9)	2 (0.9)	0.15
Master's degree	9 (1.34)	44 (1.22)	0.60	2 (0.99)	3 (1.47)	0.31
Smoking status (%)			0.000			0.61#
Current smoker	521 (77.7)	413 (11.4)		166 (57.2)	160 (55.1)	
Family history of MI (%)			0.92			0.92#
Yes	174 (25.8)	937 (26.02)		51 (25.0)	37 (18.1)	
Job status (%)			<0.001			0.90#
Employed	557 (83.1)	1160 (32.23)		155 (75.9)	156 (76.4)	
Diabetes (%)			<0.001			0.27#
Yes	59 (8.8)	619 (17.1)		27 (13.2)	20 (9.8)	
Hypertension			<0.001			0.45#
Yes	95 (14.2)	1027 (28.5)		42 (20.5)	36 (17.6)	
Blood cholesterol (mean)	172.89±37.4	187.860±39.4	<0.001	177.48±40.6	177.24±35.6	0.94*
Alcohol consumption			<0.001			0.38#
Yes	56(8.3)	90(2.5)		23(11.2)	38(18.6)	

*t-test # Chi-2

With PSM, the incidence rate per 1000 person-years in the whole study base was 3.12. In the exposed and unexposed groups, the incidence rates were 3.35 and 2.88, respectively. A similar trend was shown for cumulative incidences, as it was lower without PSM than with PSM: 3.44 in the whole group, 4.41 in the exposed group, and 2.45 in the non-exposed group (Table 2).

Table 3 displays the hazard ratios, both unadjusted and multivariable adjusted, in the whole sample (that is, without PSM) and the PSM sample. The multivariable-adjusted hazard ratio without PSM was found to be 0.73 (95% CI 0.58-0.98). In the PSM sample, it was 1.24 (95% CI 0.87-1.76). Although the latter was found to be imprecise, we cannot dismiss the point estimate, which is the most plausible value in the 95% CI function. Given the number of cases among those exposed to opium, it should be noted that the 95% CI included a null HR, probably due to the small number of myocardial infarction cases.

Discussion

In this study, the relationship between exposure to opium and the risk of heart attack in osteoarthritis patients was

Table 2. Unadjusted incidence, incidence rates and rate ratios of myocardial infarction with and without propensity score matching

Variable	Participants (n)	MI**events (n)	Cumulative incidence* (%) (95% CI)	Rate per 1000 person-years*	Cumulative incidence ratios	Rate ratios
Without PS matching						
Total	4266	86	2.01(0.6-2.6)	3.82(3.5-4.1)	1.04	0.95
Exposed to opium	670	18	2.76(1.2-3.7)	2.96(2.3-3.7)	1.43	0.74
Un-exposed to opium	3596	68	1.92(1.4-2.3)	3.99(3.6-4.3)	*	*
With PS matching						
Total	408	14	3.40(1.6-5.2)	3.12(2.5-3.8)	1.41	1.08
Exposed to opium	204	9	4.41(1.6-7.1)	3.35(2.5-4.4)	1.80	1.16
Not exposed to opium	204	5	2.45(0.3-4.5)	2.88(2.0-3.8)	*	*

*Cumulative incidence and incidence rates were calculated using the whole study base. Cumulative incidence and rate ratios are unadjusted.

Table 3. Multivariable hazard ratios in the whole sample and in the sample matched by propensity score.

Disease Exposure	Cases of myocardial infarction n=86	No myocardial infarction n=4180	HR (95% CI) without PSM	Adjusted* HR (95% CI) with PSM
Not exposed	68	3528	Reference	Reference
Exposed	18	652	0.73(0.58-0.98)	1.24(0.87-1.76)

*Adjusted for age, sex, race/ethnicity, educational level, marital status, family history of chronic disease, diabetes, blood pressure, use of steroid drugs, body mass index, blood cholesterol, smoking, and alcohol consumption.

investigated using PSM and also multivariable adjustment using Cox regression. The incidence rate of heart attack in osteoarthritis patients without PS matching was 2.96, while it was 3.35 after matching. However, the hazard ratio between heart attack and opium in osteoarthritis patients before matching with the PSM method was 0.73. With the PSM, the HR was found to be 1.24. In other words, the relation has changed from reverse to direct after control for confounding. Although PSM is regarded as reducing residual confounding,[24] the number of pairs in our study was small, and thus, multivariable adjustment of the whole study base may be closer to the true association strength. The matched sample with propensity score is almost always smaller than the original sample. Therefore, relying on significance testing to detect imbalance result in misleading interpretation of results, the findings related to non-significant differences between groups may simply be due to the reduced size of the matched sample. In sum, an increase in validity due to the PSM was, unfortunately, accompanied by a decrease in precision, which suggests that the study findings should be subjected to confirmation in future cohort studies with larger sample sizes.

Only a few studies have scrutinized the association between osteoarthritis and myocardial infarction according to opium consumption. In our study, the hazard ratio between opium consumption in individuals with osteoarthritis was found to be (1.24, 95% CI:087 to 1.76). In the study conducted by Khademi et al., in 2012, this ratio was (1.9, 95% CI:1.57 to 2.29). In a study conducted by Hae-Seok Koh et al., the hazard ratio expressing the relationship between myocardial infarction and osteoarthritis was found to be 1.24 (95% CI 1.15, 1.38).[36] Another cohort study investigated the relationship between opioid consumption and heart attack, showed that after adjustment, the hazard ratio was reported as (HR=1.26, 95% CI: 1.22-1.30). Furthermore, in the studies by Nadimi, Daraba, Sadeghian, and Masoomi, that assessed the association between opium and myocardial infarction, the odds ratios were found to be statistically significant.[20,21,37-39] Our hazard ratio results are consistent with those of previous studies, including another study using PSM, based on gender, age, geographic region, and year of osteoarthritis diagnosis, which showed a 13% increase in the strength of the association.[40] The study by Li et al. investigated the relationship between opioids and myocardial infarction, and reported a multivariable-adjusted odds ratio of 1.38.[41] In a meta-analysis conducted by Scheir et al., a significant relationship between opium consumption and myocardial infarction was reported.[42] However, in a cohort study conducted by Davoodi et al., no significant association was found, which may be due to the small sample size, short follow-up period, and lack of homogeneity.[43]

On the other hand, in the present study, to control for confounders in osteoarthritis patients, such as demographic information, family history of cardiovascular diseases, and use of medications, especially anti-inflammatory drugs, the PSM approach was used. One of the reasons for using this individual matching method was to attempt at minimizing residual confounding. PS matching tends to increase the study's efficiency (power), which was another reason why it was decided to use this approach. In general, when the covariates are confounders, matching approaches tend to increase the study precision (that is, to narrow the 95% CI) and validity.

The present study has strengths and limitations. Strengths include a relatively long follow-up and quality control procedures of the parent study.

Limitations

One of the limitations of the present study include reliance on ICD10 to identify the outcome without adjudication, which would require investigation of myocardial infarction based on hospital discharge and death certificate reviews,

and classification into definite, probable, and possible. Additionally, obtaining information on the exposure from interviews raises the possibility of information bias. Furthermore, the PS matched hazard ratio when comparing exposed group with unexposed group (Table 3) was imprecise, as the 95% CI overlapped the null value, likely due to the small number of exposed individuals who developed a myocardial infarction. On the other hand, it has been shown that the most plausible value in a 95% CI is the point estimate.[44] In addition to the aforementioned limitations, no causal inference can be made based on the results of individual observational studies, despite the use of PSM, although doing a better job at adjusting for confounding.

Conclusion

The findings of the present study suggest a potential relationship between opioid usage and myocardial infarction in individuals with osteoarthritis. Future cohort studies are neeeded to confirm these results before incorporating the findings into clinical guidelines.

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Competing Interests

The authors declare that they have no conflict of interest.

Ethical Approval

This study was approved by the Research Committee of Kurdistan University of Medical Sciences (Ethical Approval Code: IR.MUK.REC1399.285).

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