Addiction & Health

https://ahj.kmu.ac.ir
10.34172/ahj.2022.1332
Vol. 14, No. 4, 2022, 250-255

Original Article

Frequency and Predictors of Opioid Use in Rheumatoid Arthritis and Seronegative Spondyloarthropathy Patients

Maryam Sahebari[1], Kourosh Ahmadi[1], Hassan Mehrad-Majd[2], Asieh Karimani[3], Masoumeh Salari[1*]

[1]Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Clinical Research Development Unit, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Abstract

Background: Pain is one of the most challenging symptoms in patients with rheumatoid arthritis (RA) and spondyloarthropathies (SpAs), and pain relief is one of the top priorities for improving health-related quality of life. When medication therapy does not significantly reduce pain, chronic opioid consumption becomes more prominent in such patients. This study aimed to evaluate the state of opioid use in RA and SpA patients.

Methods: This cross-sectional study was performed on 316 patients with RA and spondyloarthropathies (SpAs) from January to March 2014. The convenience sampling method was used to select the participants, and by obtaining verbal consent, everyone was given 15 minutes to complete a checklist independently. Demographic and opioid use data were evaluated in terms of opioid use and its predictors. In this regard, univariate and multivariate logistic regressions were used to evaluate the predictors of opioid consumption in patients. All analyses were conducted using SPSS 21 and the significance level was set at $P<0.05$.

Findings: About 9.5% of all participants, including 8.8% of RA and 22.6% of SpA cases, were opioid abusers. In the first step of the analysis, it was observed that opioid abuse was significantly higher in men, married participants, urban residents, patients with no biological therapy, and patients with a negative family history of addiction. The most prevalent ways of drug abuse were smoking and ingestion. The results of univariate logistic regression analysis revealed SpA and other factors significantly increase the chance of opioid abuse. Furthermore, multivariate logistic regression analysis showed male gender (OR = 10.4) and negative family history of addiction (OR = 3.19) significantly affected addiction in RA and SpA patients with a 95% confidence interval.

Conclusion: Lack of suitable responsiveness to medication therapy to relieve pain, inconsistent pain evaluation, and shame of asking direct questions about addiction in RA and SpA patients may lead to opioid consumption in some cases. Seronegative SpA may make patients more prone to addiction. However, in this study, male gender and no family history of addiction were related to opioid abuse.

Keywords: Opium, Opioid, Rheumatoid arthritis, Spondyloarthropathy, Pain, Addiction

Citation: Sahebari M, Ahmadi K, Mehrad-Majd H, Karimani A, Salari M. Frequency and predictors of opioid use in rheumatoid arthritis and seronegative spondyloarthropathy patients. *Addict Health*. 2022;14(4):250-255. doi:10.34172/ahj.2022.1332

Received: December 14, 2021, **Accepted**: February 3, 2022, **ePublished**: October 29, 2022

Introduction

Rheumatoid arthritis (RA) is the most inflammatory autoimmune polyarthritis disease characterized by joint pain and destruction.[1-3] Its prevalence is 0.56% ± 0.51 in different populations.[4] Seronegative Spondyloarthropathies (SpAs) include ankylosing spondylitis, psoriatic spondylitis, reactive arthritis, and inflammatory bowel disease (IBD).[5]

One of the clinical manifestations of SpA is the involvement of axial and peripheral joints between the second and fourth decades of life with male predominance. The incidence varies from 0.2% to 1.9% in different communities.[6] Moreover, significant manifestations of SpA are inflammatory back pain at night as well as morning stiffness.[7]

Pain is one of the most challenging symptoms in patients with RA. Hence, pain relief is one of the top priorities for improving health-related quality of life. The inflammatory process in RA activates the primary afferent nerves in the joints, leading to environmental and central sensitization. Despite good disease control with anti-rheumatic drugs, joint pain remains an important problem for many RA patients.[7]

Experiencing severe pain in the active disease and progressive joint damage in those non-responsive to traditional disease modifying anti-rheumatic drugs (DMARD) are predicting factors for opioid use as powerful drugs. Pain is the main reason for 90.4% of patients with early RA to visit a healthcare professional. However, pain usually starts before the manifestations

*Corresponding Author: Masoumeh Salari, Emails: salarim@mums.ac.ir, rdrc@mums.ac.ir

of RA, leading to psychological distress, sleep disorders, and restricted activity. Moreover, pain is a determinant in assessing the disease.[8] Pain is often considered an alternative marker of inflammatory disease activity, the only reliable determinant to estimate disease activity.[9]

Current guidelines for treating RA using monotherapy or combination therapy are provided and recommend as DMARDs. Although many patients experience good disease control with DMARDs, subpopulations of patients continue to experience significant pain when disease activity is in remission or low. Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and acetaminophen are used as direct pharmacological pain-relieving treatment.[7]

When medication therapy does not significantly reduce pain in RA and SpA, opioid consumption becomes more prominent among patients. Recent cohort studies have reported that a maximum of 40% of RA patients are regular opioid users, and accordingly, the conventional rheumatic medications have a negligible effect on reducing opioid use.[10] Pain and antidepressant therapy were the most potent predictors of chronic opioid use.[11]

A study on the trend of opioid use in RA patients reported that chronic opioid consumption was 2.3% in RA patients aged 50 to 64 years, though it was 0.8% in non-RA patients in the same age group. In this study, patients treated with systemic glucocorticoids were at higher risk of chronic opioid use, though disease severity and higher disease activity indices were not significantly associated with an increased risk of chronic opioid use.[12]

However, in a study conducted to investigate the frequency of opium abuse in patients with painful diseases in Iran, a short period of pain or chronic pain was not recognized as a predictor of drug addiction.[13] In short, delay in starting an effective treatment or applying effective DMARDs makes patients prone to drug addiction.[14]

Lee et al proposed that the annual prevalence of chronic opioid use increased more than twice among RA patients (from 7.4% to 16.9% from 2002 to 2015). In addition to severe pain and antidepressant therapy as the strongest predictors of chronic opioid use, high disease activity, high disability, Medicaid insurance, and Medicare insurance have significantly affected opioid abuse. Moreover, RA medications, particularly corticosteroids and DMARDs, are associated with an increased risk of chronic drug abuse.[11]

Therefore, the abovementioned observations highlight the perception of the prevalence and predictors of opioid use in RA and SpA patients. Accordingly, the present study aimed to evaluate the predictors of drug abuse in RA and SpA patients.

Methods

This cross-sectional study was performed on 316 patients with RA (n = 251) and seronegative arthritis (psoriatic arthritis, ankylosing spondylitis, reactive arthritis, and IBDs related to SpAs) (n = 65) who visited the Rheumatic Diseases Research Center (RDRC) of Mashhad University of Medical Sciences from January to March 2014. In the pilot study, a sample was selected considering the prevalence of SpAs and RA in the study population. By obtaining verbal consent, patients over 18 years of age were selected. RA and SpA were diagnosed based on ACR/EULAR 2010 and the ASAS 2012 criteria.[15]

The exclusion criteria were liver and kidney diseases that limited the maximum dose or type of main treatment, malignancy, psychiatric illnesses (such as schizophrenia and major depression), receiving antipsychotic therapies, neuropathic pain (such as pain related to chronic radiculopathy and canal stenosis especially in patients treated with anti-neuropathic drugs), and opioid addiction before the diagnosis of the disease.

All patients were selected by the convenience sampling method. A checklist was provided to the patients to complete anonymously in 15 minutes on their own. Some questions of the checklist were not answered by a few patients. If patients were illiterate, a trained nurse helped them fill the checklist. All answers to opioid questions were evaluated in terms of opioid use, opioid type, and predictors of drug abuse. Furthermore, the patients were prescribed anti-rheumatic medications, and their accurate use was evaluated by interview. The demographic data and checklist information were analyzed using SPSS 22.

Statistical analysis

Descriptive statistics was used to describe the quantitative variables based on central tendency, dispersion indicators, and frequency distribution. For analytical statistics, student *t* test (parametric) and Mann-Whitney test (non-parametric) were utilized to analyze quantitative variables and chi-square test was used to assess the significance of differences in qualitative variables. Univariate and multivariate logistic regressions were used to evaluate the predictors of opioid use in patients. In all analytical tests, the level of significance was set at $P < 0.05$.

After scientific and statistical revision, a designed protocol was put forward and approved by the Medical Ethics Committee. All patients were informed about the goals and methodology of the study, and verbal consent was obtained from the study participants in advance.

Results

This cross-sectional descriptive and analytical study was conducted on 316 patients diagnosed with RA (n = 251) or SpA (n = 65) based on ACR/EULAR 2010 and ASAS 2012 criteria. The prevalence of drug abuse in RA and SpA patients was 8.8% and 22.6%, respectively. The mean age of participants was 47.52 ± 14.6 years, most of whom were women (76.9%). The minimum and maximum ages

of onset of opioid use were 24 and 88 years (43.10 ± 18.62). The mean duration of disease was 7.72 ± 8.02 years.

Age and disease duration were significantly higher in RA than SpA patients. The patients' characteristics according to disease type are shown in Table 1, and Table 2 represents patients' characteristics by opioid addiction/non-addiction with statistical differences. The other features evaluated in patients included the type of rheumatic disease, opioid use, method of drug abuse, type of opioid abuse over the three last months before recruiting in the study, increase or change in the type and dose of opioids to reduce pain or control disability, and use of sedatives and disease medications (traditional or biologic DMARDs). The results indicated that 9.5% of participants were opioid users. This problem was significantly higher in men, urban habitats, married cases, patients receiving traditional DMARDs therapy, and patients with a negative family history of addiction compared to women ($P=0.001$), rural habitats ($P=0.001$), single participants ($P=0.03$), patients receiving biological therapies ($P=0.001$), and patients with a positive family history of addiction ($P=0.004$), respectively. Besides, opioid smoking and ingestion were significantly more common than other drug use methods. The results of univariate logistic regression (analysis of odds ratio [OR] and confidence interval of 95%), as illustrated in Table 3, indicated that SpA, male gender, rural and urban residency, receiving only conventional DMARDs therapy, and negative family history of opioid consumption significantly increased the chance of opioid abuse in RA and SpA patients ($P<0.05$). According to multivariate logistic regression analysis with adjusting confounding variables, as shown in Table 4, male gender (OR = 10.4) and negative family history of opioid consumption

Table 1. Characteristics of patients by types of diseases

Variable		Rheumatoid Arthritis	Seronegative Arthritis	*P* value*
		Frequency(%)	Frequency(%)	
Gender	Male	39 (15.6)	32 (49.2)	$P<0.001$
	Female	211(84.4)	33 (50.8)	
Living Area	Urban	210(84)	58(89.2)	$P=0.29$
	Rural	40(16)	7(10.8)	
Education	Low literacy to high school graduated	212(85.1)	43(67.2)	$P<0.001$
	College and advanced graduated	37(14.9)	21(32.8)	
Marital Status	Single	40(15.9)	17(26.6)	$P=0.04$
	Married	211(84.1)	47(73.4)	
Opioid use	Yes	19 (8.80)	12(22.6)	$P=0.004$
	No	198 (91.20)	41(77.4)	
Methods Of consumption	Smoking	17 (89.47)	10 (83.3)	$P=0.21$
	Ingestion	1(5.2)	1 (8.3)	
	Injection	1(5.2)	0 (0)	
	Drinking or Inhalation	0 (0)	1 (8.3)	
Opioid Subtypes	Opium	11(57.8)	4(33.3)	$P=0.6$
	Methadone	1(5.26)	2(16.6)	
	Tramadol	2(10.5)	0(0)	
	Opium extract (Shireh[16])	1(5.26)	2(16.6)	
	Others (Cocaine, LSD, Heroin, Buprenorphine)	4(21)	4(33.3)	
Increase of opioid use to reduce pain	Yes	1(5.3)	4(33.3)	$P=0.02$
	No	18(94.7)	8(66.6)	
Drug diversion to reduce pain	Yes	2(10.53)	0(0)	$P=0.25$
	No	17(89.47)	12(100)	
Biologic Medications	Yes	15(6)	13(20)	$P<0.001$
	No	236(94)	52(80)	
Rheumatoid Medications	Yes	33(14.7)	6(11.5)	$P<0.001$
	No	191(85.3)	191(85.3)	
Family History of Addiction	Yes	23(12)	10(19.2)	$P=0.17$
	No	169(88)	42(80.8)	

P value* indicated the difference significance between RA and SpA about the main variable in first column.

Table 2. Characteristics of patient s by opium consumption with significant differences

Variable		Opioid use		*P* value*
		Yes	No	
Quantitative Variables		**Mean ± SD**	**Mean ± SD**	
Age		12.45 ± 43.87	13.8 ± 47.89	*P* = 0.12
Children number		Median = 2	Median = 3	*P* = 0.48
Disease duration (year)		8.2 ± 7.79	9.85 ± 8.97	*P* = 0.5
Qualitative Variables		**Frequency (%)**	**Frequency (%)**	***P* value***
Gender	Male	18(58.1)	43(17.5)	*P* < 0.001
	Female	13(41.9)	203(82.5)	
Living area	Urban	22(71)	211(85.8)	*P* < 0.001
	Rural	9(29)	35(14.2)	
Education	Low literacy/ High school graduated	26(83.9)	199(81.2)	*P* = 0.81
	College and advanced graduated	5(16.1)	46(18.8)	
Marital status	Single	5(16.1)	42(17.1)	*P* = 0.03
	Married	26(83.9)	204(82.9)	
Biologic Medications	Yes	6(19.4)	19(7.7)	*P* < 0.001
	No	25(80.6)	228(92.3)	
Family History of addiction	Yes	8(29.6)	20(10.3)	*P* = 0.004
	No	19(70.4)	175(89.7)	
Indomethacin	Yes	11 (35.4)	20 (8.1)	*P* < 0.001
	No	20 (64.6)	227 (91.9)	
Naproxen	Yes	2 (6.5)	22 (8.9)	*P* < 0.001
	No	29 (93.5)	225 (91.1)	
Diclofenac	Yes	8 (25.8)	31 (12.5)	*P* < 0.001
	NO	23 (74.2)	216 (87.5)	

* *P* value between indices of patients with/without consumption of opioids

(3.19) had a significant effect on drug abuse in patients ($P < 0.05$).

Discussion

The results of the current study indicated 9.5% of all RA and SpA patients were opioid users, and opioid use was significantly higher in men, married patients, urban residents, patients receiving traditional DMARDs therapy, and patients with a negative family history of substance abuse. Opioid smoking and ingestion were the most common ways of drug abuse. The univariate logistic regression analysis of odds ratio and confidence interval (95%) confirmed that SpA, male gender, living in urban areas, non-use of biological medications, and negative family history of opioid use significantly increased the chance of opioid consumption in RA and SpA patients. According to multivariate logistic regression, male gender and negative family history of substance abuse significantly affected opioid abuse in patients.

In an analysis of opioid use in RA patients, Day and

Table 3. Odds ratio and 95% Confidence Interval of univariate logistic regression in determination of factors affecting opioid use

variable	OR(95% CI)	*P* value
Men/women	6.53(2.98-14.34)	< 0.001*
Non-graduated/Graduated	1.2(0.43-3.29)	0.72
Single/Married	0.93(0.33-2. 57)	0.89
Seronegative Arthritis /RA	0.32(0.14-0.72)	0.006
Urban living area	2.46(1.05-5.79)	0.03*
Treatment strategy without biologics	2.88(1.05-7.87)	0.03*
Negative Family History of addiction	3.68(1.42-9.94)	0.007*
Age	0.97(0.95-1.006)	0.12
Children number	0.97(0.81-1.15)	0.75
Disease duration (year)	1.01(0.97-1.05)	0.48

**P* value < 0.05 is Significant Level

Table 4. Odds ratio and 95% confidence interval from multivariate logistic regression in determination of factors affecting opioid use

variable	OR(95% CI)	*P* value
Men/women	10.14(3.56-28.90)	< 0.001*
RA/Seronegative Arthritis	1.26(0.34-4.63)	0.72
Urban living area	2.18(0. 7-6.73)	0.17
Treatment strategy without biologics	1.66(0.4-6.91)	0.48
Negative Family History of addiction	3.19(1.03-9.87)	0.04*
Age	0.97(0.94-1.01)	0.24

**P* value < 0.05 is Significant Level

Curtis revealed the reason for using opioids, especially in the early stages of RA, is the low effect of DMARDs on severe pain and inflammation in patients.[10] These findings are compatible with those of the present study suggesting that treatment with only traditional DMARDs has a risk of initiating opioid consumption.

In the study by Lee et al, chronic opioid use in RA patients increased from 7.4% to 16.9% between 2002 and 2015. Factors associated with chronic opioid consumption were severe pain with a score of more than 60 on a scale of 0 to 100, antidepressant use, clinical disease activity index of more than 22, and lack of pain control after biologic initiation. Moreover, they claimed that patients' self-reported addiction rate is usually less than the actual rate.[11] Although the pain level before the onset of the disease was not questioned in the present study, the assessment of opioid consumption showed significant growth in opioid use to reduce the pain level.

Amin-Esmaeili et al studied the prevalence of illicit drug use disorders in Iran according to DSM-V criteria and concluded that opioid use disorders, especially opium, are the most common type of illicit drug use disorders in Iran. The prevalence of 12-month illicit drug use disorders was 2.44% in the general population. It was also observed that the risk of drug abuse disorders was greater in men and previously married participants, than in currently or never married ones and those of lower socioeconomic

status.[17] Statistics show that the prevalence of substance abuse among the population aged 15 to 64 years in Iran was 2.65%. Moreover, according to the Iranian Anti-Narcotics Headquarters, the rate of addiction in Khorasan is 2.7%. Mashhad is the capital of Khorasan province, where the present study was conducted. Therefore, compared to the prevalence of addiction in the general population of the country and the province where the study was conducted, the rate of addiction in patients in this study was higher (9.5% of 316 patients). This study aimed to evaluate the physician's correct estimation of pain control in two different diseases; therefore, a healthy control group did not help achieve this goal.[18,19]

As expected, opioid use has a high prevalence in people with painful diseases, accounting for a large percentage (40% to 64.4%) of the general population[17,20] in Iran as in other societies. There is a higher risk of drug abuse in married men and women with lower socioeconomic status as indicated in the studies by Amin-Esmaeili et al,[17] Abshenas-Jami et al,[21] and Wada et al[22] which was similar data in our province and in line with the present study.[19]

Zamora-Legoff et al reported that 40% of patients with RA and 24% of non-RA participants were opioid users in 2014. Furthermore, patients with RA are 1.5 times more likely to use opioid than non-RA patients. They suggested this figure is significantly greater than that seen in an opioid-burdened general population, and this will even increase in the coming years.[12] Nevertheless, the present study showed 8.80% of RA patients and 22.6% of SpA patients were opioid users, which is incompatible with the results of the study by Zamora-Legoff et al. The lower opioid use ratio in RA patients in the present study could be justified by the procedures of prescribing medications and intensive treatment in RA,[23] which seem to be different in SpA patients.

Comparing the use of NSAIDs in the two groups of drug users and non-drug users, the use of NSAIDs was significantly higher in patients with SpA than in the RA group (Table 2). Various studies assessed the effects of long-term use of NSAIDs in patients with chronic pain and indicated high use of these drugs in SpA. The old treatment of prescribing these drugs as the first line of treatment and also the lower price of these drugs compared to specialized drugs, along with its effectiveness in reducing the symptoms of these patients, leads to more consumption and, consequently, failure to respond to these treatments poses a great challenge for them, which leads them to stronger drugs and opioid use.[24,25]

Pascual-Ramos et al assessed motivations for inadequate persistence with DMARDs in early RA. They concluded that difficulty finding those medications and their high prices would affect patients' compliance. Thus, patients tend to use available and inexpensive substances that reduce their pain. Opioids, especially opium, have these motivation features.[26] In this regard, the findings of the present study on the importance of arthritis medications' costs and accessibility are similar to the results of Pascual-Ramos and colleagues' study, which identified low socioeconomic status as a risk factor for drug abuse.

Limitations and Strengths

To the best of the researchers' knowledge, no other study was conducted in Iran to investigate the prevalence and predictors of opioid consumption in patients with RA and seronegative SpAs. Hence, this study is a kind of pilot study that provides valuable and practical information to design and implement more extensive studies. Moreover, assessing opioid use before and after the diagnosis of diseases revealed the effect of specific therapies' adequacy and the alteration of opioid types or dosage for pain control. Regarding the fact that patients' self-report can affect the findings of opioid consumption prevalence, it is recommended to apply a simple diagnostic test such as urine analysis in a future study that enhances the accuracy of results. It is also suggested to evaluate the level of pain and disease activity and longer periods of follow-up as was done in some other studies. Therefore, it is beneficial to assess disease activity and pain by completing a questionnaire on the VAS scale.

Conclusion

Although the number of female participants was more than males in the present study, the results showed that men were more likely to use opioids. This can be explained by the fact that RA is more common than SpAs in women. Men with SpA are more prone than those with RA to use opium because of more pain and later and more difficult diagnosis. On the other hand, social issues and personal restrictions on women, and perhaps easier access to drugs for men, also might lead to more opioid use in men.

Acknowledgments

This article reports the results of a thesis for medical physician degree approved under the code 930210. The authors would like to appreciate the Research Council of Mashhad University of Medical Sciences and all patients for their kind cooperation.

Author Contributions

MSah: Designing the study, visiting the patients and gathering data, interpreting data, revising the intellectual content, revising the final manuscript; KA: Gathering data, interpreting data, revising the comments; MSal: Designing the study, writing the primary draft of the manuscript, gathering data, analyzing data, revising the final manuscript; AK: Gathering data, interpreting data; HMM: Analyzing data, revising the final manuscript.

Conflict of Interests

The authors declare that they have no competing interests.

Ethics Approval

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Ethics code: IR.MUMS.REC.1393.153).

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