Comparison of the Effects of Passiflora Incarnata and Piroxicam in opioids withdrawal-Induced Myalgia and Anxiety: A randomized Clinical Trial

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Abstract

Background: Non-steroidal analgesics are the most commonly used analgesics for pain relief in opioids induced withdrawal. One of the herbal remedies that reduce muscle pain, anxiety, and fatigue is *Passiflora Incarnata* (*P.incarnata*). In this study, we compared Piroxicam and *P. incarnata* in withdrawal-induced myalgia and anxiety.

Materials and Method: This was a clinical trial carried out on 43 candidate patients for maintenance treatment with methadone. The individuals were randomly divided into two groups. The control group was prescribed piroxicam capsule (10 mg every 12 hours), while the intervention group received drops of *P. incarnata* (10-15 drops three times a day), until symptoms of withdrawal were resolved (7 to 10 days). In the first, 3rd, sixth, and ninth days of treatment, the patient's vital signs, myalgia (visual acuity), and anxiety (Beck test) were recorded and analyzed.

Results: The results of this study revealed that the flower drops resulted in a reduction in myalgia (mean score of 5.4± 0.79 on the first day decreased to 1. 3 ±0.5 on the ninth day), but there was no significant difference in comparison with Piroxicam (p=0.705). Further, *P. incarnata* significantly reduced the anxiety caused by withdrawal (p =0.001).

Conclusion: *P. incarnata* drop can be used to reduce the pain and anxiety caused by the drug's withdrawal.

Keywords: *Passiflora Incarnata, Myalgia, Anxiety, Addiction withdrawal.*

Introduction

Today, drug addiction and opioids poisoning are social, health, and political problem involving most countries of the world, especially the developing countries[1--4]. Opioids use has so many direct or indirect adverse on human health[4-13]. Unfortunately, drug addiction and poisoning in adolescence and youngsters also are increasing[2,4,14]. Methadone is a proper replacement for withdrawal situation [9-12]. Withdrawal is also accompanied by important consequences such as anxiety, stress, nervous seizures, and severe myalgia [15]. Tolerating myalgia is hard and unbearable for an addicted person.

Non-steroids are one of the most commonly used analgesics to reduce the pain caused by withdrawal. While based on Iranian traditional medicine, one of the herbal remedies that reduce myalgia, anxiety, and

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grouch is *Passiflora incarnata* [15].

Passiflora incarnata L. (Passifloraceae) is used in traditional herbal medicines, which has shown different therapeutic properties [16, 17]. Interestingly, in India, it is used to treat morphine's dependence [18,] while in Africa, it is used for its sedative and analgesic properties [19,20]. The *P. incarnata* is not narcotic or addictive, so it is used in tea, pills, and drops for treatment of sleep disorders, restlessness, irritability, and anxiety [15, 21,22]. In recent years, many studies have been conducted on the effective substances of this plant as anti-anxiety and toxicity properties [23-25], and as a benzodiazepine-receptor agonist [24]. Animal studies have also revealed that *P. incarnata L*. has been effective in controlling the pain caused by alcohol withdrawal [20]. Meanwhile, other studies have indicated that when the plant is used in the treatment, it reduces the need for opioids in addicts [26].

Piroxicam is a potent inhibitor of the cyclooxygenase enzyme with some serious adverse effects [27]. Regarding the effects of analgesic drugs and very few studies on the effectiveness of *P. incarnata* plant in some common complications of drug addiction withdrawal, this study was conducted to compare the effects of Piroxicam and *P. incarnata* on myalgia and anxiety due to addiction withdrawal.

Materials and Method

This project was a single-blind clinical trial performed on clients of addiction treatment centers in Sabzevar city. Conscious informed consent form was obtained from all participants in the study. The project was also registered as IRCT20170404033202N6 at the Iranian Center for Clinical Record Registration. Forty-three patients who wanted to replace use of opium with methadone were included into the project with personal satisfaction. The subjects were divided into two groups using simple random method. Piroxicam (10 mg once every 12 hours) was prescribed to one group (n = 20), while the other group (n = 23) received *P. incarnata* drop (10-15 drops based on the weight three times a day) [28,29] which were consumed until the withdrawal symptoms resolved and methadone dosage stabilization (between 7 and 9 days).

The patients received methadone and analgesic every day, until resolution of withdrawal symptoms and methadone dose stabilization. Every three days (1st, 3rd, sixth and ninth), the patient's vital signs were based on a self-designed checklist; the amount of muscle pain was completed based on the Visual analog scale (VAS) and anxiety based on the Beck test. If the visual score of pain was more than 9, then pain reliever would begin and be excluded from the study and another person would be replaced. The Beck Anxiety Questionnaire has a high validity rating [29]. The total score of this questionnaire lies within the range from 0 to 63 [30]. The pain was measured by the researcher using Visual Analog Scale (VAS), standardized for pain assessment.

Finally, the data were collected and analyzed by SPSS20 through independent T-tests, paired t-test, and repeated measurement.

Results

In the study of 43 individuals selected in this study, the mean age of the subjects was 35.7 ± 3.5 years in the two groups, with a total of at least 28 years and a maximum of 45 years old, where most patients were 30 to 42 years old. The mean age in *P. incarnata* group was 37 ± 4 years and 34.5 ± 3 years in the Piroxicam group (Table 1).

All subjects were male, so in terms of the threshold of pain, there is no confounding. The frequency of drug use was between 1 and 3 times a day, with an average of 2.4 ± 0.2 mg/dl in the intervention group, and in the control group 2.3 ± 0.2 times a day. Most of the patients used opium three times a day. The mean amount of consumed drug (opium) was 1.28 ± 0.5 in the intervention group, and 1.21 ± 0.5 in the control group. The duration of opium addiction varied from 1 to 4 years, with an average of 2.68 years. The number of drug intake days (passiflora or piroxicam) was between 7 and 9 days until all the symptoms of pain were resolved. A total of 41% of people had 8 days of taking medication (pain reliever). The mean of Piroxicam and Passiflora use was 8 ± 0.79 and 7.96 ± 0.76, respectively ($p = 0.85$). The mean score of pain and anxiety before the intervention was not significantly different between the two groups ($p > 0.05$).

In the Piroxicam group, the mean score of the VAS on the first day was 0.86 ± 4.7, and on the ninth day, it was 0.51 ± 0.1, which showed a significant decrease ($p < 0.001$). In the *P. incarnata* group, pain intensity was 0.79 ± 5.4 on the first day and decreased to 0.5 ± 1.3 on the ninth day ($p < 0.001$).

Comparison of the two groups on the 9th day in the Piroxicam group revealed a mean pain score of 0.51 ± 1.4

and in passiflora group 0.5 ± 1.3 (p = 0.705). The mean anxiety score in the Piroxicam group on the first day was 0.5 ± 3.50 and on the ninth day in the same group, which was 0.5 ± 2.4 (p= 0. 001). In the passiflora group, the average anxiety score on the first day of treatment was 0.5 ± 3.62, and on the ninth day of treatment, it was 0.34 ± 1.1 (p= 0.010). Comparing the effect of two drugs on anxiety, the results indicated that the mean anxiety score in the Piroxicam group was 0.5 ± 2.4 on the ninth day, and 0.34 ± 1.1 in the passiflora group (p = 0.001). Based on the results of repeated measurement analysis, pain and anxiety severity at different times in the *P. incarnata* group and piroxicam group were statistically significant (P <0.001). Further, the results of Bonferroni post hoc test showed that all the times in each group had a significant difference in two groups (P <0.05) (Table2)

Table 1: Comparison of demographic variables and data related to addiction in two groups of Piroxicam and Passiflora incarnata

		Passiflora incarnata group	Piroxicam group
Age (year)		4 ± 37	3 ± 5/34
Gender	Male	23	20
	Female	0	0
Duration of opium addiction (year (		2.81 ± 0.5	2.56 ± 0.5
Amount of opium use (g)		1.28 ± 0.5	1.21± 0.5
Drug use frequency per day		2.4 ± 0.2	2.3 ± 0.2

Table 2: Comparison of severity of pain and anxiety in the designated days in two groups of passiflora and piroxicam

Variable	**Anxiety Score**					**Intensity of pain**				
Time Group	**1st day**	**3rd day**	**6th day**	**9th day**	**repeated measurement test results**	**1st day**	**3rd day**	**6th day**	**9th day**	**repeated measurement test results**
Passiflora group (n=23)	3.6±0.5*	1.43±0.59*	1.13±0.34*	1.1±0.34*	F=264.87 P<0.001	5.4±0.79*	2.96±0.7*	1.83±0.5*	1.3±0.5*	F=184.29 P<0.001
Piroxicam group (n=20)	3.5±0.5*	3.2±0.52*	2.9±0.3*	2.4±0.5*	F=36 P<0.001	4.7±0.86*	2.65±0.6*	1.9±0.6*	1.4±0.51*	F=82.84 P<0.001

* Significant difference between each day and other times

Discussion

The results of this study suggested that drops of *P. incarnata* reduce the anxiety and myalgia caused by withdrawal. There was no statistical difference in the treatment of mediation between the two treatments at the end of the study. To the best of our knowledge, this study is the first clinical trial on the effect of *P. incarnata* in the treatment of anxiety and myalgia caused by opium withdrawal. Compared to other similar studies that had examined the effect of passiflora on other diseases, there was a similarity between our study and those articles in terms of the sample size, duration of drug use as well as the results, which are in line with the findings of this study. Other studies showed the positive effects of Passiflora drops in reducing the anxiety similar to benzodiazepines; the greatest effects of *P. incarnata* was from day seven onward [31], [33]. Some animal studies have also suggested the agonist effects on GABA-a in creating anti-anxiety effects [23,24]. Others also argue that *P. incarnata* extracts may be helpful in the control of withdrawal symptoms of alcohol consumption [30]. Some studies have suggested that opioid withdrawal leads to a significant reduction in the analgesic threshold and induction of withdrawal hyperalgesia [35]. Previous studies have reported the clinical role of active ingredients of this substance synergistically [17]. It is reasonable that the pain reliever and anti-anxiety properties of this plant can be attributed to the synergistic action of GABA

A , GABA B and its effect on opioid receptor [20, 36]. A considerable part of the scientific literature has provided pre-clinical evidence of the beneficial properties of *P. incarnata* in the treatment of addictive behaviors related to substances such as amphetamine, nicotine, cannabis, ethanol, and benzodiazepine [34,37,38].

Conclusion

The results suggested that *P. incarnata* drops as well as Piroxicam can reduce the severity and anxiety and myalgia caused by withdrawal.

Conflict of Interests: None.

Funding: The research project of this manuscript was supported financially by Sabzevar University of Medical Sciences

Ethical Clearance: This study was approved by the ethics committee of Sabzevar university of medical sciences.

References

1. Roshani B, Jalali A, Bidhendi S, Ezzati E, Mahboubi M. Study the causes of relapse among Iranian drugs users in Kermanshah. Life Science Journal. 2014;11(1s):66-71.
2. Karrari P, Mehrpour O, Afshari R, Keyler D. Pattern of illicit drug use in patients referred to addiction treatment centres in Birjand, Eastern Iran. J Pak Med Assoc. 2013 Jun;63(6):711-6.
3. Mehrpour O. Addiction and seizure ability of tramadol in high-risk patients. Indian J Anaesth. 2013 Jan;57(1):86-7.
4. Alinejad S, Zamani N, Abdollahi M, Mehrpour O. A Narrative Review of Acute Adult Poisoning in Iran. Iran J Med Sci. 2017 Jul;42(4):327-346.
5. Ghaderi A, Vahdati-Mashhadian N, Oghabian Z, Moradi V, Afshari R, Mehrpour O. Thallium exists in opioid poisoned patients. Daru. 2015 Aug 1;23:39.
6: Hayatbakhsh MM, Oghabian Z, Conlon E, Nakhaee S, Amirabadizadeh AR, Zahedi MJ, Darvish Moghadam S, Ahmadi B, Soroush S, Aaseth J, Mehrpour O. Lead poisoning among opium users in Iran: an emerging health hazard. Subst Abuse Treat Prev Policy. 2017 Oct 5;12(1):43.
7: Nakhaee S, Mehrpour O. Opium addiction as new source of lead poisoning: An emerging epidemic in Iran. EXCLI J. 2018 Jun 4;17:513-515.
8: Alinejad S, Aaseth J, Abdollahi M, Hassanian-Moghaddam H, Mehrpour O. Clinical Aspects of Opium Adulterated with Lead in Iran: A Review. Basic Clin Pharmacol Toxicol. 2018 Jan;122(1):56-64.
9: Alinejad S, Ghaemi K, Abdollahi M, Mehrpour O. Nephrotoxicity of methadone: a systematic review. Springerplus. 2016 Dec 9;5(1):2087.
10. Alinejad S, Kazemi T, Zamani N, Hoffman RS, Mehrpour O. A systematic review of the cardiotoxicity of methadone. EXCLI J. 2015 May 5;14:577-600.
11. Ghasemi S, Izadpanahi S, Yaghoubi MA, Brent J, Mehrpour O. Methadone associated long term hearing loss and nephrotoxicity; a case report and literature review. Subst Abuse Treat Prev Policy. 2019 Nov 6;14(1):48.
12. Soroosh D, Neamatshahi M, Zarmehri B, Nakhaee S, Mehrpour O. Drug-induced prolonged corrected QT interval in patients with methadone and opium overdose. Subst Abuse Treat Prev Policy. 2019 Feb 20;14(1):8.
13: Farzaneh E, Mehrpour O, Alfred S, Moghaddam HH, Behnoush B, Seghatoleslam T. Self-poisoning suicide attempts among students in Tehran, Iran. Psychiatr Danub. 2010 Mar;22(1):34-8.
14. Mehrpour O, Abdollahi M. Poison treatment centers in Iran. Hum Exp Toxicol.2012 Mar;31(3):303-4.
15. Ben-Erik van Wyk, Michael Wink. Medicinal Plants of the World. An Illustrated Scientific Guide to Important Medicinal Plants and their Uses. Portland, OR, USA: CABI; 2017.
16. Dhawan K, Dhawan S, Sharma A. Passiflora: a review update. Journal of ethnopharmacology. 2004;94(1):1-23.
17. Miroddi M, Calapai G, Navarra M, Minciullo P, Gangemi S. Passiflora incarnata L.: ethnopharmacology, clinical application, safety and evaluation of clinical trials. Journal of ethnopharmacology. 2013;150(3):791-804.
18. Ingale A, Hivrale A. Pharmacological studies of Passiflora sp. and their bioactive compounds. African Journal of Plant Science. 2010;4(10):417-26.
19. Neuwinger HD. African traditional medicine: a dictionary of plant use and applications. With supplement: search system for diseases. the

University of California: Medpharm; 2000.

20. Schunck RVA, Macedo IC, Laste G, de Souza A, Valle MTC, Salomón JL, et al. Standardized Passiflora incarnata L. extract reverts the analgesia induced by alcohol withdrawal in rats. Phytotherapy research. 2017;31(8):1199-208.
21. Jawna-Zboińska K, Blecharz-Klin K, Joniec-Maciejak I, Wawer A, Pyrzanowska J, Piechal A, et al. Passiflora incarnata L. improves spatial memory, reduces stress, and affects neurotransmission in rats. Phytotherapy Research. 2016;30(5):781-9.
22. Hajimehdipoor H, Rezazadeh S, Hadjiakhoondi A, Pirali Hamedani M, Rezaee A, Zahedi H, et al. Comparative and differential study of Passiflora incarnata L. and Passiflora caerulea L. in raw plants and pharmaceutical dosage forms. Journal of Medicinal Plants. 2007;3(23):65-71.
23. Bennati E. Identification, by thin-layer chromatography, of liquid extract of Passiflora incarnata. Bollettino chimico farmaceutico. 1967;106(11):756-60.
24. Azimaraghi O, Yousefshahi F, Khatavi F, Zamani MM, Movafegh A. Both oral passiflora incarnata and oxazepam can reduce pre-operative anxiety in ambulatory surgery patients: a double-blind, placebo-controlled study. Asian J Pharm Clin Res. 2017;10(8):331-4.
25. Bennati E, Fedeli E. Gas chromatography of fluid extract of Passiflora incarnata. Bollettino chimico farmaceutico. 1968;107(11):716.
26. Akhondzadeh S, Kashani L, Mobaseri M, Hosseini S, Nikzad S, Khani M. Passionflower in the treatment of opiates withdrawal: A double□blind randomized controlled trial. Journal of clinical pharmacy and therapeutics. 2001;26(5):369-73.
27. Nouri, Nasrin; Mohammad Yahya, Elham; Zohreh Vand, Fatemeh. A Comprehensive Dictionary of Iranian Generic Drugs. 1: Rafi's Andishe; 2015. p. 1267.
28. Wolfman C, Viola H, Paladini A, Dajas F, Medina JH. Possible anxiolytic effects of chrysin, a central benzodiazepine receptor ligand isolated from Passiflora coerulea. Pharmacology Biochemistry and Behavior. 1994;47(1):1-4.
29. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. Journal of consulting and clinical psychology. 1988;56(6):893.
30. Ashtiani M. Psychological Tests, Personality Assessment, and Mental Health. Besat, Tehran: Basat Publication. 2009.
31. Akhondzadeh S, Naghavi H, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: A pilot double-blind randomized controlled trial with oxazepam. Journal of clinical pharmacy and therapeutics. 2001;26(5):363-7.
32. Movafegh A, Alizadeh R, Hajimohamadi F, Esfehani F, Nejatfar M. Preoperative oral Passiflora incarnata reduces anxiety in ambulatory surgery patients: a double-blind, placebo-controlled study. Anesthesia & Analgesia. 2008;106(6):1728-32.
33. Rahimi M, Modaresi M, Sajjadian I. The feasibility of replacing diazepam with passion flower's extract for reducing anxiety Der Pharma Chemica. 2016;8(3):60.
34. Dhawan K. Drug/substance reversal effects of a novel tri-substituted benzoflavone moiety (BZF) isolated from Passiflora incarnata Linn.–a brief perspective. Addiction biology. 2003;8(4):379-86.
35. Yang H-Y, Wu Z-Y, Bian J-S. Hydrogen sulfide inhibits opioid withdrawal-induced pain sensitization in rats by down-regulation of spinal calcitonin gene-related peptide expression in the spine. International Journal of Neuropsychopharmacology. 2014;17(9):1387-95.
36. Aman U, Subhan F, Shahid M, Akbar S, Ahmad N, Ali G, et al. Passiflora incarnata attenuation of neuropathic allodynia and vulvodynia apropos GABA-ergic and opioidergic antinociceptive and behavioural mechanisms. BMC complementary and alternative medicine. 2016;16(1):77.
37. Dhawan K, Kumar S, Sharma A. Comparative anxiolytic activity profile of various preparations of Passiflora incarnata linneaus: a comment on medicinal plants' standardization. The Journal of Alternative & Complementary Medicine. 2002;8(3):283-91.
38. Capasso A, Sorrentino L. Pharmacological studies on the sedative and hypnotic effect of Kava kava and Passiflora extracts combination. Phytomedicine. 2005;12(1-2):39-45.