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Peer Review

Journal of Comprehensive Pediatrics
Article DOI: https://doi.org/10.5812/compreped.113199
Published in: Journal of Comprehensive Pediatrics: 12(4) ; e113199

Peer Review Report for "Pruritus, as a Neglected Symptom, in Opioid Poisoning in Children"

Author(s): fariba farnaghi, Marjaneh Abbasi Ghadi, Latif Gachkar, Hossein Hassanian Moghaddam

Review Timeline:

Submit Date:	23 Jan 2021
Revised Date:	3 Oct 2021
Accepted Date:	16 Oct 2021

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE : Reviewer — 12 Apr 2021

Dear EIC
This study is done and written in a professional way
After native English review its convenient for publication.

REFEREE : Reviewer — 17 May 2021

Thank you for presenting this manuscript. But I have many questions about this presentation:

We are not allowed to use any abbreviation word without definition for the first time: CBC, CNS

There is no standardization for some words throughout the text (for example: (%) or (number and %) in the text, especially in abstract section)
Citing references should be noted at the end of sentences [....(..).].

Abstract:
Aim of study was not complete and clear.
Number of participant should be noticed in method section (no in results section).
Age of allocation should be mentioned.
Line 2, results section, beginning of sentences with number is not correct (57%...)
Introduction:
Line 1 need rephrases: (All kinds of opioid poisonings are common and fatal poisoning in children in Iran). Introduction is so weak. Unrelated sentences must be omitted. The background should summarize the purpose and the rationale for the study. It should neither review the subject extensively nor contains data or conclusions of the study.
Methods:
What is sampling methods? Number of study participants?
Inclusion and exclusion criteria were incomplete. Pl defines precisely and clearly.
Inclusions and exclusions criteria must be mention to first paragraph.
How did you calculate the sample size? Explain it. Number of participant should be noticed in method section (no in results section). Age of allocation should be mentioned.
You explain which parametric or non-parametric tests were used for which variables? Be defines precise and clear. Methodology and statistical analyses of this study is not appropriate. In this type of study, at first, correlation testing should be used (two-tailed Pearson's correlation coefficient analyses, or r) and if one variables was significant (relationships) then, use spearman test to find OR or HR.
There are many confounding factors in the studies about" postoperative fever Risk factors in children with congenital heart disease". How did you include the confounding factors in the results? Clearly define all potential confounders and effect modifiers.
Describe statistical methods.
Results:
Line 1-2, first paragraph should be omitted. That is repetitive and incorrect place (mention in methods section).
Legends and title of figures must be placed at the bottom of the figure (no in top).
Table 4 and 5 were confusing. Describe statistical methods at the bottom of tables.
Table 5 need explanations, precisely and clear. How did you find pruritus to be related with apnea, nausea and so on?
Discussion:
In the discussion part you should write the main(s) finding(s) (novelty) at first and then allude to other studies. . It concentrates on the new and important aspects of the study and the achieve conclusions
Limitation and recommendation should be mentioned in the last paragraph of discussion.

References:

References did not arrange according to the rules of the journal.

Best regards

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

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You can read the authors' responses to the reviewers' comments in the next page.

Reviewers' Comments and revised article according to their comments:

"Pruritus and related factors in opioids poisoning in children."

Reviewer 1:
Dear EIC
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Reviewer 2:
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References:
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Pruritus ,as a neglected symptom, in opioids poisoning in children.

Abstract:

Background: Opioids poisoning is common and fatal childhood poisoning in Iran with nonspecific, hidden ,vague and misleading clinical manifestations in some . **Objective**: The aim of this study was to investigate and emphasize on pruritus , as a neglected and helpful symptom in this important poisoning.

Methods: In this cross-sectional study, one hundred pediatrics patients (< 14 years) with opioids poisoning who referred to Loghman Hakim Hospital, Tehran-Iran from April 2018 to April 2019 were enrolled the study. Demographic data including age, sex, type of poisoning, clinical manifestations including pruritus, its onset, location, duration and therapy, also laboratory findings including Complete Blood Count(CBC) and Eosinophilia recorded in patient-specific information forms. The collected data were analyzed using SPSS 21 software.

Results: The patients' mean age was 43.4±31.4months. Fifty-seven(57%) of them were male. Fifty-two(52%) of them reported Pruritus that in 84% observed in face. In 31% of children, itching resulted in skin scratches. The most common clinical manifestations were CNS depression (93%) respiratory suppression (68%), vomiting (52%), pruritus (52%) and meiosis (51%). There was no significant relationship between pruritus and gender, age, laboratory findings, family history of addiction and allergy. There was a significant statistical relationship between the pruritus and meiosis, apnea, vomiting, cyanosis, and redness of the skin . Pruritus controlled with naloxone in all of our patients.

Conclusion: According to the results of presented study, Pruritus is common and helpful clinical manifestations in children with opioids poisoning that helps the physician for correct diagnosis specially in hidden clinical scenarios.

Key words: Opioids, Poisoning, Children, Pruritus.

Background:

Opioid poisonings are common and fatal poisoning in children in Iran. (1,2) Classic opioid toxidrome of respiratory depression, Central nervous system(CNS) depression and meiosis can produce severe morbidity and even death. (3) Opioids can also cause multiple nonspecific findings in various organ systems . (4).This signs and symptoms are similar to many other CNS depressant agents like Barbiturates ,Clonidine ,Baclofen, Sedative-hypnotics ,Ethanol coma and some other toxins. (5) Pruritus is a symptom of opioid poisoning that is not occurred in other CNS depressants poisoning thus it is helpful in clinical diagnosis.

Sometimes the true history of opium poisoning hide by parents because of some legal, familial, social and some other factors and wide range of clinical manifestations and differential diagnosis make it a difficult scenario. Opioid-poisoned patients are particularly appropriate as clinical diagnosis . Even in rare situations in which the assay results are available rapidly, the fact that several various classes of opioids and nonopioids can produce similar opioid effects limits the use of laboratory tests(5). Pruritus is poorly investigated in pediatric opium poisoning. The pathogenesis of opioid-induced pruritus is still not fully known, but two different mechanisms have been proposed: peripheral and central by histamine thus may be associated with hypotension , flushing and rhinorrhea .(5) Facial areas innervated by the trigeminal nerve are mostly affected, probably due to the high concentration of opioid receptors in the nucleus of the trigeminal nerve.(6)

Typically, patients scratch the nose, paranasal area and upper part of the face, although generalized pruritus has also been reported.(7). Xenobiotics commonly implicated in neurally mediated itch include tramadol, codeine, cocaine, morphine, butorphanol , and methamphetamine. (5)Several treatment modalities have been tried for opioid-induced pruritus (OIP), most indicated a significant reduction in the frequency and severity of itching with naloxone. (8)

Objectives:

Pruritus is a helpful symptom for making correct diagnosis of this important poisoning but this valuable sign is frequently neglected by both parents and physicians. The aim of our study is to emphasize and evaluation of pruritus and related factors in opioid poisoning in children.

METHODS:

This cross-sectional descriptive study conducted on one hundred pediatric (< 14 years) patients presenting with opioid poisoning in Loghman Hakim Hospital (referral poison center) from April 2018 to April 2019in Tehran-Iran. The inclusion criteria were age under14 years and definitive diagnosis of opioids poisoning confirm by history, compatible physical examination and positive urine rapid test and ; the exclusion criteria were patients with indefinite diagnosis , Co- ingestion and negative urine toxicology test . Sample size: Because we hadn't find pervious similar study for sample size calculation , the participants were enrolled according to convenience simple sampling. Using a self-made questionnaire, demographics characteristic, type and amount of poisoned opioid agent, clinical manifestations, pruritus and its location, presentation time, duration and treatment modalities, also related major Paraclinic parameters mainly Complete blood count and Eosinophilia were documented for each patient and statistically analyzed. The data were analyzed by descriptive and analytical statistics (ANOVA and t-test) with SPSS software version 21 , chi squared when comparing two percentages and *t*-test when comparing two means. The level of significance was set at a p value of less than 0.05.This study was approved by Ethics Committee of Shahid Beheshti University of Medical Sciences.Ethic code: IR.SBMU.MSP.REC.1398.439.

RESULTS:

Out of 100 studied patients ,57% were male and 43%were female with mean age of 43.4±31.4months ,near half of them were between 1-3 years (Table 1).

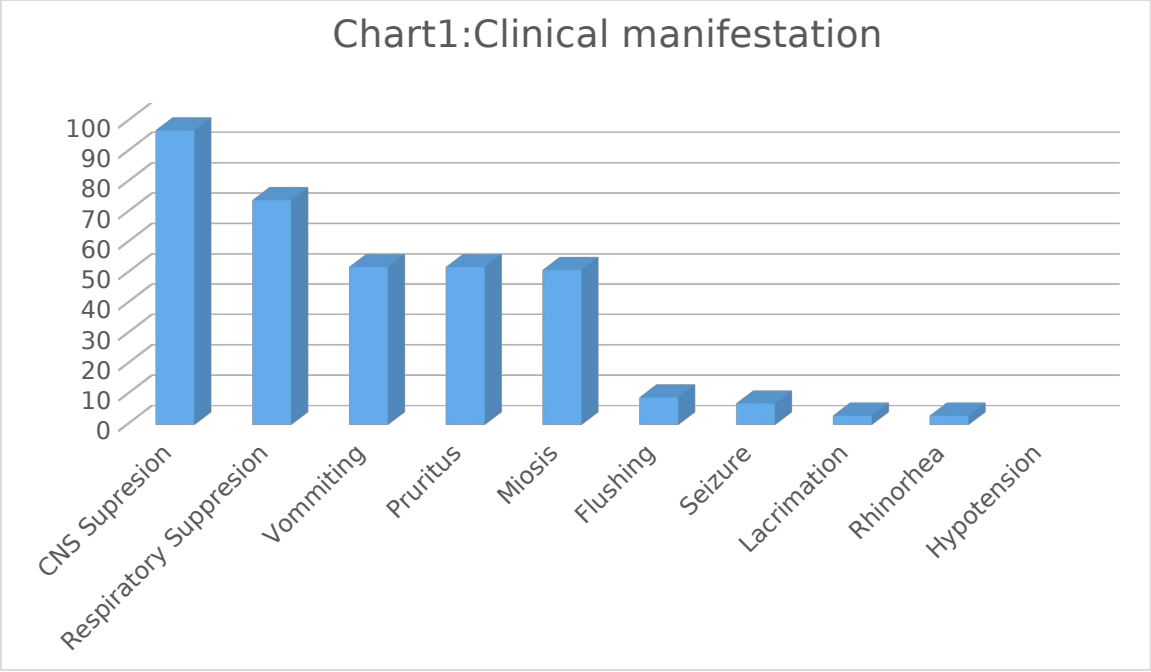
Table1- Age distribution among studied patients.

Age (year)	no(%)
<1y	16(16%)
1-3y	**48(48%)**
3-5y	23(23%)
>5y	13(13%)
Total	100%

Type of opioids poisoning shows in Table2, all of them were unintentional poisoning, the greatest proportion of poisonings was methadone (n=65, 65%) especially methadone syrup (90%). Amount of ingested methadone was uncertain in 80% of cases, and in the remainder the ingested methadone dose was 30.6±11milligrams although in majority of them the reported ingested methadone dose was small amount.

Eighteen percent of our cases had positive history of living with addicted parents (completely their father). The most frequent clinical manifestation in our patients were CNS depression (n=93, 93%) respiratory suppression (n=68, 68%), vomiting (n=52, 52%) and pruritus (n=52, 52%), illustrated in Chart 1.

Chart 1: Clinical manifestation among studied patients.



Pruritus was observed in 52% of our patients and most of them (84%) happened in face,only12% had generalized itching.

Pruritus leading to scratch & abrasion in 16(31%) of cases.

The pruritus begun between 15minutes and 360 minutes after ingestion, mean 90.1±8.9minutes, most of them (84%) occurred at face and the mean duration of this sign was5.5±4.7 hours and lasted from 30 minutes to 24 hours.

As showed in Table 2 ,Analytic analysis of cases with pruritus in relation with sex, age and ingested opium showed that this differences were not statistically significant.

Table 2- Analytic analysis of cases with or without pruritus in relation with sex, age and ingested agent.

		Patient with Pruritus n=52(52%)[a]	**Patient without Pruritus n=48(48%)**	**P value**
Sex	**Female**	21(41%)	22(45%)	0.70[b]
	Male	31((59%	26(55%)	
Mean age		44.8±36.3	42.4±34.3	0.38[b]
Ingested Opioids	Methadone	33	32	Not significant[c]
	Opium	7	6	
	Tramadol	5	4	
	Heroin	3	2	
	Buprenorphine	2	3	
	Codeine	2	1	

[a]Values are expressed as No. (%) unless otherwise indicated ,[b]Chi-squared test and[c] *independent t*-test

The relation between type of opioids agent and pruritus in our patients was not statistically significant. (P value =0.62). Patients with positive allergy history (n= 9,19%) were prone to opioid –induced pruritus. (P value =0.04).

Table3 showed the relationship between Pruritus and clinical manifestations, pruritus was

statistically significant relation with Respiratory suppression ,Vomiting, Meiosis and histamine symptoms like Flushing, Lacrimation and Rhinorrhea .

Table3- Analytic analysis of cases with or without pruritus in relation with clinical manifestations

Sign/Symptom	Patient with Pruritus n=52(52%)[a]	Patient without Pruritus n=48(48%)	P value[b]
CNS depression	48(92%)	45((94%)	0.41
Respiratory suppression	(96%)50	(50%)24	0.05
Vomiting	33(64%)	19(40%)	0.009
Meiosis	34(65%)	17(35%)	0.003
Flushing	9(17%)	0	0.002
Seizure	5(10%)	2(4%)	0.26
Lacrimation	3(6%)	0	0.08
Rhinorrhea	3(6%)	0	0.08
Hypotension	1(2%)	0	0.32

[a]Values are expressed as No. (%) unless otherwise indicated.[b] *independent t*-test.

In most of our patient (58%)CBC including WBC & differentiation was normal, and eosinophilia not reported for any of them. All cases of opium-induced pruritus in our study controlled with naloxone without any additional therapy except naloxone.

DISCUSSION:

This study is unique in the sense that we didn't find any article emphasizing this symptom in opium poisoning. According to the results of the present study, pruritus is a common and helpful sign in acute opioid poisoning ,in our study more than half of them had pruritus but we did not find any related research about this important sign in children. Opium and methadone poisoning as a common and fatal childhood poisoning in Iran (9,10,2).Alizadeh A et al about the epidemiological pattern and recent changes of acute pediatric poisoning in

Mashhad during 2011- 2013 showed that this poisoning is common in children but changed from traditional opium to methadone poisoning. (11)

Adam Reich et al reported that pruritus is a common adverse effects of chronic opioid treatment and they found that the risk is increased when opioids are administered epidurally or intraspinally, in present study we found that pruritus was common and observed in 52% of children with acute oral opioids poisoning.(7)Also Benson JL et al declared that Opioid-induced pruritus (OIP) is one of the most common adverse effects of oral and neuraxial opioids.(12)

Amy H. Huang Et al assessment for relative rates of pruritus associated with commonly drugs in adult showed that among all drugs investigated, heparin (1.11%), trimethoprim–sulfamethoxazole (1.06%), and calcium channel blockers (0.92%) were associated with the highest rates of pruritus, their study conducted in adult and in chronic drug users.(**13).**Szarvas S et al reported the induced of OPI after intrathecal and epidural opioids varies between 30% and 100%. (14) In present study we found that more than half of methadone poisoned patient had pruritus, but in one study conducted by Sharif MR and Nouri S_ about Clinical signs and symptoms and Laboratory Findings of Methadone Poisoning in Children ,they didn't report any cases of methadone induced pruritus . This difference may because that pruritus didn't tell or consider by parents or physicians .(15) Other researches about clinical manifestation of opium poisoning in children and adults such as Nasim Zamani et al that conducted a study on 228 infants and 82 toddlers opium poisoned cases admitted to Loghman Hakim Hospital 2001 - 2009 showed that the most usual sign of opium poisoning was meiosis (90%) followed by a decreased level of consciousness (88.4%), bradypnea (28.4%) and seizure (10.3%) without any cases with pruritus.(16).Also Ghaemi N study results showed similar results.(17)

In our study frequently observed clinical manifestations were CNS depression(93%), Respiratory suppression(74%), Vomiting(52%), Pruritus(52%), Meiosis(51%) . Sixteen patients experienced skin abrasion . We had not find any reported article about pruritus in acute opioids poisoning in children. Pruritus in all of our patients controlled by naloxone , Miller JL_et al reported the effectiveness of the use of pure opioid antagonists for the prevention and treatment of opioid-induced pruritus as a common adverse effect of therapeutic use of oral opioid medications in adults.(7)

Frost J and Spigset O. declared that pruritus is a common adverse effect of opioids although not harmful but can be troublesome with no proven pathogenesis and μ-opioid receptor antagonist or the serotonin 5-HT3 receptor antagonists ondansetron has documented effect for therapy. (18) Eosinophilia was not reported in our patients, may be because that CBC in our patients did not performed manually. Tahereh Haghpanah et al reported that Eosinophil count showed no difference in opium or heroin addicted adults with control group.(19)

The treatment of opioid-induced pruritus remains a challenge. Szarvas S et al reported that various drugs including antihistamines, 5-HT3 receptor antagonists, opiate-antagonists, propofol, nonsteroidal anti-inflammatory drugs, and droperidol, have been studied for OIP.(14)A meta-analysis on thirteen studies including 1138 patients showed that naloxone act as an effective treatment and prophylaxis of opioid-induced pruritus, nausea, and vomiting .(20) Similar to our study that Pruritus in all of the cases easily controlled by naloxone.

Limitation of our study is that quantitative blood test for opioids are not available in our hospital and further study by prospectively designed multicenter studies and larger sample size is recommended.

CONCLUSION:

According to the results of present study; Pruritus is a common, neglected and helpful symptom of acute opioid poisoning in children that easily controlled with opioids antagonist; naloxone**.** Based on the results of this study, most cases of children with acute opioids toxicity experienced pruritus mainly in face and nose. This sign helps physicians in diagnosis of this serious poisoning in hidden or obscure clinical situations.

ACKNOWLEDGMENTS:

The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation and assistance throughout the study.

Footnotes

- **Authors' Contribution:** All authors collaborated in all stages of the design, data collection, and writing of the article. Dr. Farnaghi, as the responsible author, submitted the article.
- **Conflict of Interests:** The authors report no conflicts of interest.
- **Ethical Approval:** This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences.
- **Funding/Support:** The authors declare that there was no funding/support.
- **Informed Consent:** Informed consent was obtained from the patient’s parents.

References:

1. Soltaninejad K, Hassanian-Moghaddam H, Shadnia S. Methadone related poisoning on the rise in Tehran, Iran. Asia Pacific Journal of Medical Toxicology. 2014;3(3):104-9.

2. Shadnia S, Rahimi M, Hassanian-Moghaddam H, Soltaninejad K, Noroozi A. Methadone toxicity: comparing tablet and syrup formulations during a decade in an academic poison center of Iran. Clinical toxicology. 2013;51(8):777-82. DOI: 10.3109/15563650.2013.830732 [PMID: 23972442]

3. Kliegman RM, Geme JS. Nelson Textbook of Pediatrics E-Book: Elsevier Health Sciences; 2019.

4. Shan Yin MMB, James F Wiley Opioid intoxication in children and adolescents. Up ToDate. 2018.

5. Hoffman RS, Howland MA, Lewin NA, Nelson LS, Goldfrank LR. Goldfrank's Toxicologic Emergencies, Tenth Edition (ebook): McGraw-Hill Education; 2014.

6. Reich A, Szepietowski J. Opioid-induced pruritus: an update. Clinical and Experimental Dermatology: Clinical dermatology. 2010;35(1):2-6. doi: 10.1111/j.1365-2230.2009.03463.x.

7. Reich A, Ständer S, Szepietowski JC. Drug-induced pruritus: a review. Acta dermato-venereologica. 2009;89(3):236-44. doi: 10.2340/00015555-0650.

8. Miller JL, Hagemann TM. Use of pure opioid antagonists for management of opioid-induced pruritus. American Journal of Health-System Pharmacy. 2011;68(15):1419-25. . PMID: 21785031 DOI: 10.2146/ajhp100475

9. Pirzadeh Z, Jamshidi M, Mollamohammadi M. Acute Poisoning in Children Referred to Qazvin Children Hospital (2009 to 2012). J Compr Ped. 2016;7(4):e40099. doi: 10.17795/compreped-40099.

10. Mansori K, Soori H, Farnaghi F, Khodakarim S. A case-control study on risk factors for unintentional childhood poisoning in Tehran. Medical journal of the Islamic Republic of Iran. 2016;30:355. .[PMID: 27453885].
11. Alizadeh A, Asoudeh MZ, Abdi F, Moshiri M, Mood MB, Etemad L. Epidemiological pattern of acute pediatric poisoning in Mashhad, Iran during 2011-2013. International Journal of High Risk Behaviors and Addiction. 2017;6(2). doi: 10.5812/ijhrba.33707.
12. Benson JL, Campbell HE, Phillips CN. Opioid-induced pruritus. The Consultant pharmacist : the journal of the American Society of Consultant Pharmacists. 2015;30(4):221-7. . DOI: 10.4140/TCP.n.2015.221. [PMID: 25893700]
13. Huang AH, Kaffenberger BH, Reich A, Szepietowski JC, Ständer S, Kwatra SG. Pruritus Associated with Commonly Prescribed Medications in a Tertiary Care Center. Medicines. 2019;6(3):84. DOI: 10.3390/medicines6030084. [PMID**:** 31382689]
14. Szarvas S, Harmon D, Murphy D. Neuraxial opioid-induced pruritus: a review. Journal of clinical anesthesia. 2003;15(3):234-9. . DOI: 10.1016/s0952-8180(02)00501-9 .[PMID: 12770663].
15. Sharif MR, Nouri S. Clinical signs and symptoms and laboratory findings of methadone poisoning in children. Iranian journal of pediatrics. 2015;25(1). doi: 10.5812/ijp.176.
16. Zamani N, Sanaei-Zadeh H, Mostafazadeh B. Hallmarks of opium poisoning in infants and toddlers. Tropical doctor. 2010;40(4):220-2. [PMID: **2**44940**5].**
17. Ghaemi N, Alikhani S, Bagheri S, Sezavar M. A Cross Sectional Study of Opioid Poisoning in Children at a Tertiary Center. Asia Pacific Journal of Medical Toxicology. 2016;5(4):115-8. DOI: 10.4045/tidsskr.12.0539 .[PMID: 23076488]
18. Khansari M, Sohrabi M, Zamani F. The useage of opioids and their adverse effects in gastrointestinal practice: a review. Middle East journal of digestive diseases. 2013;5(1):5.[PMID: 24829664]
19. Haghpanah T, Afarinesh M, Divsalar K. A review on hematological factors in opioid-dependent people (opium and heroin) after the withdrawal period. Addiction & health. 2010;2(1-2):9. [PMID: **2**44940**5].**
20. He F, Jiang Y, Li L. The effect of naloxone treatment on opioid-induced side effects: A meta-analysis of randomized and controlled trails. Medicine. 2016;95(37). DOI: 10.1097/MD.0000000000047 [PMID: 27631221].

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Revision (1)

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Revision (2)

Reply to Reviewers

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Reviewers' Comments and revised article according to their comments:

Reviewer 2:

The great effort in improving the manuscript is highly appreciated. Most points mentioned have been changed by authors. The following points are of concern and minor suggestions are marked in the following. Several important questions were asked, especially in the methods section, but no precise answer was given.

In abstract section, P value should be mentioned for main results.1 (Line 19-20 & line 95-6)

The authors said:" There was a significant statistical relationship between the pruritus and meiosis, apnea, vomiting, cyanosis, and redness of the skin..." but cyanosis was not seen in the text!? 2(line 18-9)

There is no standardization for some words throughout the text and abstract. For example: Did the respiratory suppression mean apnea? In results section you said apnea but in the text respiratory suppression?!!! 2(line 81) [Similarly, flushing and redness of the skin?!3(table 3)

In introduction, paragraph 1, line 4-5 it is suggested that the authors briefly mention the drugs that are widely used today that cause similar side effect "selective serotonin reuptake inhibitors (SSRIs). You should be used newer references such as [Which of available selective serotonin reuptake inhibitors (SSRIs) is more effective in treatment of premature ejaculation? A randomized clinical trial. Int Braz J Urol. 2019; 45 (6): 1209-1215. doi: 10.1590/S1677-5538.IBJU.2019.0121 [PMID: 31808410]" and

[Comparative study of on-demand and daily use of sertraline in treatment of premature ejaculation: A randomized clinical trial. Asian Journal of Urology. 2021; 8(2), 209-214. https: // doi.org/10.1016/j.ajur.2019.10.002].You're right but I have not find newer references about this item.

The authors have repeatedly used the term of "relation or relationship". It had been mentioned before that in this type of study, correlation testing should be used (two-tailed Pearson's correlation coefficient analyses, or spearman (r). With the tests performed in the text (chi squared and t-test), we can only notice the significant difference or not between the two groups (pruritus and without pruritus), not notice the relation. Pl corrects that in the manuscript at all.4(line18),6(line 68)

Legends and title of figures must be placed at the bottom of the figure (no in top). (chart 1) 5(Chart1)

The authors said that "The level of significance was set at a p value of less than 0.05" but in results you noticed that " pruritus was statistically significant relation with Respiratory suppression ,Vomiting, Meiosis and histamine symptoms like Flushing, Lacrimation and Rhinorrhea" .

P value by Respiratory suppression (0.05); Lacrimation (0.08)and Rhinorrhea (0.08) were not significant. Correct the results (in the text and abstract).done as **(≤ 0.05)** *6(line 68)*

Thank you

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Revision (2)

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Revision (3)

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Comments to the Author:
I reviewed the manuscript again; totally. The great effort in improving the manuscript is highly appreciated. Most points mentioned have been changed by authors. The following points are of concern and suggestions are marked in the following. Important questions were asked, but no precise answer was given.

1-It is suggested that in introduction, paragraph 1, line 4-5 the authors briefly mention the selective serotonin reuptake inhibitors (SSRIs) that are widely used today which cause similar side effects that are commonly consumed in the community. But you said but I have not find newer references about this item. It suggested these valuable articles about side effects of SSRI. In table no 3 of these articles, clearly mentions the most common side effects of these drugs that are similar to the side effect on narcotics and others CNS depressant agents like Barbiturates ,Clonidine ,Baclofen, Sedative-hypnotics ,Ethanol coma and some other toxins. You should be used newer and valuable references such as [Which of available selective serotonin reuptake inhibitors (SSRIs) is more effective in treatment of premature ejaculation? A randomized clinical trial. Int Braz J Urol. 2019; 45 (6): 1209-1215. doi: 10.1590/S1677-5538.IBJU.2019.0121 [PMID: 31808410][PMCID:PMC6909853] " and [Comparative study of on-demand and daily use of sertraline in treatment of premature ejaculation: A randomized clinical trial. Asian Journal of Urology. 2021; 8(2), 209-214. doi:10.1016/j.ajur.2019.10.002 . [PMID: 33996478][PMCID:PMC8099698].

For example paragraph 1, line 4-5, the authors noticed that: "Opioids can also cause multiple nonspecific findings in various organ systems (4). This signs and symptoms are similar to many other CNS depressant agents like Barbiturates ,Clonidine ,Baclofen, Sedative-hypnotics ,Ethanol coma, selective serotonin reuptake inhibitors (SSRIs) and some other toxins. The most common side effect of these drugs were drowsiness, fatigue, constipation, nausea, loss of appetite, decrease sexual desire and urinary retention and so on. Pruritus is a symptom of opioid poisoning that is not occurred in other CNS depressants poisoning thus it is helpful in clinical diagnosis".

2- How did you calculate the sample size? Which formula did you use?
In methods section you said: "Sample size: Because we hadn't find pervious similar study for sample size calculation , the participants were enrolled according to convenience simple sampling". This was not acceptable.
Two valuable and standard formulas are used for cross sectional study 1- n=([p(1-p)]×(z1-α/2) ²)/d^2 And 2- n=(2(Z1-α/2+ Z1-ß)^2 σ ²)/d^2 By reviewing the previous studies, σ=?,ß=?, α=5% and d= ?
Or you could use Morgan table for calculating of participants.

3- In table 2, "Not significantc" change to "0.62".

Dear Reviewer:

Thank you so much for your careful review :

1-About SSRIs;

SSRIs poisoning because of their serotoninergic toxidrome are not mistakable with opium poisoning, this patients are agitated , mydriasis ,tachycardia,.. that differentiate this poisoning from opium poisoning.

2-sample size calculation:

Because we hadn't find pervious similar study for sample size calculation , one hundred participants were enrolled according to convenience simple sampling using α=95%,P=50% and D=10%.

3-Done

Best regards.

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Revision (3)