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ORIGINAL RESEARCH

Comparing Two Naloxone Tapering Methods in Management of Methadone Intoxication; a Quasi-experimental Study

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Abstract: **Introduction:** Even though naloxone is the main treatment for methadone poisoning treatment there are controversies about the proper method of its tapering. This study aimed to compare two methods in this regard. **Methods:** This study was a prospective, single-blind pilot quasi-experimental study on non-addicted adult patients poisoned with methadone. Patients were randomly divided into 2 groups. In one group, after stabilization of respiratory conditions and consciousness, naloxone was tapered using the half-life of methadone and in the other group, naloxone was tapered using the half-life of naloxone. Recurrence of symptoms and changes in venous blood gas parameters were compared between groups as outcome. **Results:** 52 patients were included (51.92% female). 31 cases entered Group A (tapering based on methadone's half-life) and 21 cases entered Group B (tapering based on naloxone's half-life). The two groups were similar regarding mean age (p = 0.575), gender distribution (p = 0.535), the cause of methadone use (p = 0.599), previous medical history (p = 0.529), previous methadone use (p = 0.654), drug use history (p = 0.444), and vital signs on arrival to emergency department (p = 0.054). The cases of re-decreasing consciousness during tapering (52.38% vs. 25.81%; p = 0.049) and after discontinuation of naloxone (72.73% vs. 37.50%; p = 0.050) were higher in the tapering based on naloxone half-life group. The relative risk reduction (RRR) for naloxone half-life group was -1.03 and for methadone half-life group was 0.51. The absolute risk reduction (ARR) was 0.27 (95% confidence interval (CI) = 0.01-0.53) and the number needed to treat (NNT) was 3.7 (95% CI= 1.87- 150.53). There was not any statistically significant difference between groups regarding pH, HCO_3, and PCO_2 changes during tapering and after naloxone discontinuation (P > 0.05). However, repeated measures analysis of variance (ANOVA), showed that in the tapering based on methadone's half-life group, the number of changes and stability in the normal range were better (p < 0.001). **Conclusion:** It seems that, by tapering naloxone based on methadone's half-life, not only blood acid-base disorders are treated, but they also remain stable after discontinuation and the possibility of symptom recurrence is reduced.

Keywords: Naloxone; Methadone; Drug Users; Poisoning; Drug Tapering

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1. Introduction

Methadone is a synthetic opioid substance that was developed in the 1940s as a pain reliever. This drug is the most widely used treatment for opioid dependence and has been used worldwide for more than 40 years under the name methadone maintenance treatment (MMT)(1). Previous studies have shown that MMT reduces the risk of crime, illicit

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drug use, morbidity, and mortality, and improves behaviors in patients compared to opioid users (2-4). Methadone toxicity is rising among those accidentally exposed to it, which results in increased mortality.

Methadone intoxication results in clinical manifestations such as loss of consciousness, respiratory depression (bradypnea/apnea), cardiovascular disturbances (hypotension, cardiac arrhythmia, and QT prolongation), nausea, vomiting, seizures, and miosis. The duration of intoxication with methadone is long compared to other opioid substances (5-7).

The most widely used antidote in acute opioid poisoning is the administration of naloxone(8-10). Pharmacologically, naloxone is a pure opioid receptor antagonist. By a competitive mechanism, it blocks the binding of opioid substances to the receptor. After initiation, naloxone is tapered based on the patient's condition and subsequently discontinued. If naloxone is administered in high doses or repeat doses are administered too rapidly, naloxone can precipitate acute opioid withdrawal syndrome. Signs of this syndrome include vomiting, tachycardia, shivering, sweating, and tremor (11). Serious adverse effects can include pulmonary edema, hypertensive emergencies, ventricular dysrhythmias, delirium, seizures, and death (11-15). Even if an immediate, life-threatening adverse event does not occur, patients with acute opioid withdrawal are agitated and usually require sedative drugs, putting them at risk for aspiration, and recurrent respiratory depression (11).

Despite the seriousness of methadone poisoning, there are no specific recommendations in medical textbooks for how to administer naloxone. Naloxone is accepted as a first-line antidote, in some sources as a PRN (pro re nata) regimen, and as a continuous intravenous infusion. The length of treatment and its dosage is unknown. 12 to 18 hours, 0.25-6.25 mg/h up to 25 mcg/kg/h is recommended (16-18). On the other hand, there is no discussion about how to taper naloxone after the patient's condition is stable.

This is a dilemma in clinical toxicology. Trying to find a safer method in this regard, this study aimed to compare tapering based on naloxone half-life and based on methadone half-life for treatment of methadone intoxicated patients in emergency department.

2. Methods

2.1. Study design and setting

This study was a prospective, single-blind, and pilot quasi-experimental study, which was conducted on non-addicted patients poisoned with methadone who were referred to Loghman Hakim Hospital, Tehran, Iran, during 2021-2022. The study protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences with the code IR.SBMU.RETECH.REC.1400.1038. Participants signed informed written consent forms. This article was also registered in the Iranian Registry of Clinical Trials with number: IRCT20220305054196N1.

2.2. Participants

Methadone-poisoned patients over 18 years of age, who presented with a reduced level of consciousness with or without respiratory depression, didn't have an addiction, and were not under MMT treatment were included. Patients with methadone poisoning with other hypnotic sedatives, patients who were discharged against medical advice, and patients who experienced withdrawal syndrome symptoms after receiving naloxone or did not need naloxone were excluded from the study.

2.3. Data gathering

Methadone poisoning was confirmed by history and urine drug tests. The patient's addiction history was recorded based on the information given by the patient or his/her companions. Concomitant poisoning was diagnosed using symptoms, history, and results of urine tests.

Upon arrival, vital signs (blood pressure, heart rate, breathing rate, body temperature, level of consciousness, and percentage of oxygen saturation) were recorded and a blood sample was collected for venous blood gas (VBG) analysis. The amount of methadone consumed was recorded. Then the patients were treated with naloxone.

pH, PCO_2 (Partial pressure of carbon dioxide), and HCO_3 (Bicarbonate) concentrations were recorded before starting tapering, during tapering, and after discontinuation of naloxone. The time of improvement of symptoms (Reaching the percentage of oxygen saturation above 90%), return of consciousness (patient being awake and aware of surroundings and identity), and resolution of respiratory depression was recorded. The final condition of the patient was checked. The endpoint of tapering was the amount of naloxone administered being less than 0.1 mg/hour and the stability of the PCO_2 level and the patient's consciousness.

2.4. Intervention

Patients were allocated to the groups based on random numbers table. Patients were clinically evaluated without knowing which method was used for Naloxone tapering. In one group, after the patient's condition was stable, naloxone was tapered using the half-life of naloxone (decreasing the dose of naloxone by 50% every 3 hours), and in the other group, naloxone was tapered using the half-life of methadone (decreasing the dose of administered Naloxone by 50% every 6 hours). After discontinuation of naloxone, patients were monitored for 8 hours. Tapering methods were designed based on the relative estimation of the half-life of naloxone

and methadone, as well as the experiences of researchers in clinical treatment.

2.5. Outcomes

Time to recovery, the re-decreasing consciousness, and change in VBG parameters (pH, HCO_3, and PCO_2) during tapering and after discontinue of naloxone were compared between groups as outcome.

2.6. Statistical analysis

Considering 95% confidence interval and alpha error of 5%, the sample size was considered to be 50 cases. SPSS software version 21 was used to analyze the information. The population normality was assessed using Kolmogorov-Smirnov test, then independent and paired t-test were used for parametric data and chi-square for non-parametric data. P<0.05 was considered as the level of significance. Regression models were used for controlling confounding variables.

3. Results

3.1. Baseline characteristics of studied cases

52 patients were included, 27 (51.92%) were female and 25 (48.07%) were male. 31 cases entered Group A (tapering based on the methadone half-life) and 21 cases entered Group B (tapering based on the naloxone half-life). Most of the patients (61.54%) had taken methadone due to suicide, and had no history of illness and drug or methadone use. Six people had a history of suicide attempts with methadone (4 people in group A and 2 people in group B).

Table 1 compares the baseline characteristics of studied patients between groups. The mean age of the patients was 28.68±10.9 years in group A, and 28.38±11.5 years in group B (p = 0.575). There was no difference between the two groups regarding gender distribution (p = 0.535), cause of methadone use (p = 0.599), previous medical history (p = 0.529), previous methadone use (p = 0.654), drug use history (p = 0.444), and vital signs on arrival to emergency department (p = 0.045). None of the patients needed intubation. Although all patients were candidates for admission to intensive care unit (ICU), only 3 patients were treated in ICU. All patients recovered and were discharged from the hospital.

3.2. Comparing the outcomes

Table 2 and figure 1 compare the studied outcomes between the two groups. The cases of re-decreasing consciousness during tapering (52.38% vs. 25.81%; p = 0.049) and after discontinue naloxone (72.73% vs. 37.50%; p = 0.050) were higher in the tapering based on naloxone half-life group. The relative risk of re-decreasing of consciousness during tapering was 0.49 and 2.03 in methadone half-life and naloxone half-life groups, respectively. The relative risk reduction (RRR) was -1.03 for naloxone half-life group and 0.51for methadone half-life group. The absolute risk reduction (ARR) was 0.27 (95% CI = 0.01-0.53) and the number needed to treat (NNT)

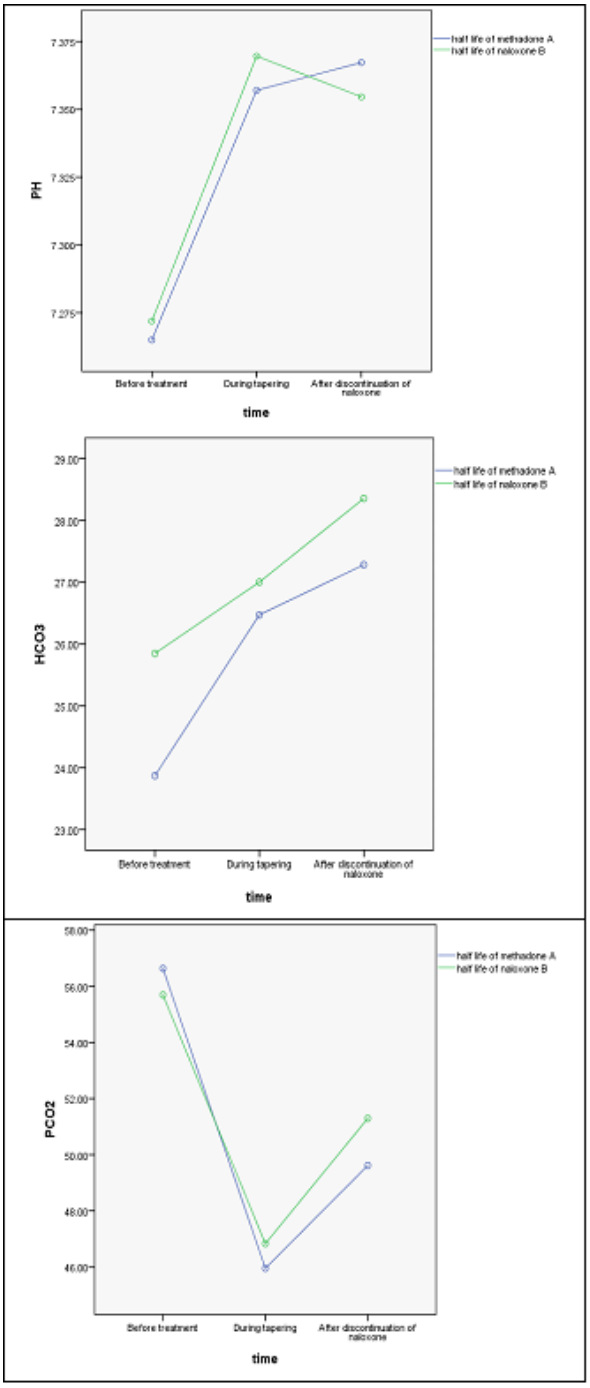

Figure 1: Comparing the pH, HCO_3, and PCO_2 changes in the patients poisoned with methadone between the two groups of naloxone tapering based on methadone half-life and naloxone half-life.

Table 1: Comparing the baseline characteristics of studied cases between the two groups

Variable	Tapering based on the half-life of		P-value
	Methadone (n = 31)	Naloxone (n = 21)	
Gender			
Male	16 (51.6)	9 (42.9)	0.535
Female	15 (48.4)	12 (57.1)	
Age (years)			
Mean ± SD	28.7±11.0	28.4±11.5	0.575
Consumption due to suicide attempt			
Yes	20 (64.5)	12 (57.1)	0.599
Medical history			
Previous use of methadone	6 (19.3)	2 (9.5)	0.654
Previous disease	3 (9.7)	2 (9.5)	0.529
Drug use	6 (19.3)	4 (19.1)	0.444
Smoking	8 (25.8)	6 (28.6)	0.684
Alcohol consumption	1 (3.2)	0 (0.0)	
Marijuana consumption	2 (6.4)	0 (0.0)	
Taking psychotropic pills	2 (6.4)	1 (4.8)	
Vital signs			
Systolic BP (mmHg)	112.6±13.6	109.8±8.5	0.054
Diastolic BP (mmHg)	74.1±13.1	71±7.5	0.054
PR (Pulses/ minute)	90.93±16.5	80.11±22.06	0.65
RR (Breaths/ minute)	17.8±7.8	15.87±2.8	0.173
Glasgow coma scale	12.7±2.3	12.3±2.7	0.289
O2 saturation (%)	86.6±14.2	87±19.3	0.393
Treatment in ICU			
Yes	1 (3.2)	2 (9.5)	0.339
Naloxone dose (mg)			
Loading	1.97±1.4	1.28±0.7	0.067
Maintenance	1.07±0.64	0.81±0.37	0.073
VBG findings			
Primary PH	7.26±0.09	7.27±0.09	0.558
Primary HCO_3	23.87±5.7	25.84±3.6	0.187
Primary PCO_2 (mmHg)	56.63±15.4	55.69±11.2	0.162

Data are presented as mean ± standard deviation (SD) or frequency (%). BP: blood pressure, ICU: intensive care unit, PR: pulse rate, RR: respiratory rate, VBG: venous blood gas.

was 3.7 (95% CI= 1.87- 150.53).

There was not any statistically significant difference between groups regarding pH, HCO_3, and PCO_2 changes during tapering and after naloxone discontinuation ($p > 0.05$). However, repeated measures ANOVA, shows that in the tapering with methadone half-life group, the number of changes and stability in the normal range were better ($p < 0.001$).

4. Discussion

We found that although the recovery time of decreased consciousness was not significantly different in the two methods, the return of central nervous system (CNS) depression during dose reduction was significantly different. In patients tapered based on half-live of naloxone, the number of cases with re-decreasing CNS depression was higher than the other group and this re-decreasing occurred most significantly in time of discontinuing naloxone. The number of changes in pH, HCO_3 and PCO_2 in the group tapering based on the methadone half-life was better during dose reduction and after naloxone discontinuation.

Methadone is a synthetic opium that is used as a pain reliever and in the maintenance treatment of addicted patients, and its consumption is increasing (19). Accidental use or overdose of methadone can cause multiple organ damage in both humans and animals (20-22). Methadone has significant tissue distribution; tissue levels may exceed plasma levels. The lipophilic nature of methadone allows for rapid absorption, long duration of action, and slow release from tissues into the bloodstream. This causes wide variations in the half-life, giving a range of 2 to 65 hours (23).

Opioid and methadone overdose syndrome is a true medical emergency. Naloxone is mainly administered intravenously at the same time as other supportive measures (24, 25). Naloxone has a rapid onset of action, its maximum serum concentration is reached 2 minutes after intravenous injec-

Table 2: Comparing the outcomes of studied cases between groups

Outcomes	Tapering based on the half-life of		P-value
	Methadone (n = 31)	Naloxone (n = 21)	
pH			
During tapering	7.36±0.03	7.36±0.03	0.738
After discontinuing Naloxone	7.37±0.04	7.35±0.05	0.239
HCO_3 (mmHg)			
During tapering	26.47±3.6	27±3.4	0.684
After discontinuing Naloxone	27.28±4.9	28.35±2.8	0.050
PCO_2 (mmHg)			
During tapering	45.9±10.4	46.8±4.2	0.074
After discontinuing Naloxone	49.6±11.01	51.3±7.8	0.318
Re-decreased consciousness			
During tapering	8 (25.81)	11 (52.38)	0.049
After discontinuing Naloxone	3 (37.5)	8 (72.73)	0.050
Time to recovery (day)			
From respiratory depression	0.29±0.5	0.43±0.5	0.085
Final outcome			
Recovery	31 (100.0)	21 (100.0)	0.596

Data are presented as mean ± standard deviation (SD) or frequency (%). The blood gas analysis is reported based on venous sample.

tion, 10 minutes after intramuscular injection, and 15 to 30 minutes after intranasal administration (26). Naloxone is extensively metabolized in the liver, its serum half-life is about 30 to 90 minutes (27).

Although naloxone is relatively safe in naïve persons, it should be used with caution in chronic methadone users who experience overdose. High blood levels of naloxone can trigger drug withdrawal symptoms in people who have previously been exposed to methadone. The onset of withdrawal symptoms can increase an individual's risk of relapse (28, 29). We conducted this study on non-addicted subjects to cover this major confounding factor and not have to discontinue naloxone due to withdrawal syndrome.

Unfortunately, none of the studies have worked on the tapering method. Given that naloxone has a much shorter half-life than methadone (90 minutes vs. 65 hours), re-depression of the CNS may occur due to the slow release of methadone from the tissues into the blood after discontinuation of naloxone (23, 30). We observed that in the taper group based on the half-life of naloxone, the cases of re-decreasing consciousness were significantly higher (52.38%) and 72.73% of them showed decreased consciousness after discontinuation of naloxone. This could be due to the patient being naloxone-free when there is still methadone in her/his body and it is slowly released from the storage places and causes brain effects.

Dr. Yazdanbakhsh and his colleagues have conducted a study on the comparison of two naloxone-based regimens in the treatment of methadone overdose. They randomly divided 80 patients with methadone overdose into two groups: the infusion and the PRN groups. The severity of deprivation syndrome was evaluated after 30 minutes, 3 hours and 12 hours of treatment in both groups. Their results showed that administering naloxone as PRN reduces the amount and severity of withdrawal syndrome (31).

Dr. Khosravi et al. conducted a study, comparing two naloxone regimens. 100 opioid-dependent patients with signs/symptoms of methadone overdose were included in the study. Patients were allocated to groups treated based on Tintinalli protocol (group 1) or Goldfrank diet protocol (group 2). Group 1 received naloxone at a dose of 0.1 mg every two to three minutes, while group 2 received naloxone at an initial dose of 0.04 mg, which was increased to 0.4, 2, and 10 mg every two to three minutes until respiratory depression was reversed. They then compared them in terms of reversal of toxicity and risk of complications. Finally, their results showed that the gradual titration of naloxone with the Tintinalli protocol can reduce major complications compared to the Goldfrank regimen (32). Neither of the two studies discussed the issue of naloxone tapering.

It may seem that the gradual discontinuation of naloxone based on the half-life of naloxone reduces the length of stay in the hospital and the overall cost of the patient, but our results showed that firstly, there was no significant difference in ICU admission, the initial dose of naloxone, and the maintenance dose between the two groups. The risk of re-reducing consciousness was higher in the group tapered based on the half-life of naloxone.

5. Limitations

The limitations of this study were the small number of patients in each group, the lack of equality of patients in the two groups, the failure to examine the trend of all clinical factors and symptoms in the two groups, and the lack of blinding of the main investigators during the study.

6. Conclusion

It seems that, by tapering naloxone based on methadone's half-life, not only blood acid-base disorders are treated, but they also remain stable after discontinuation and the possibility of symptom recurrence is reduced.

7. Declarations

7.1. Acknowledgments

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7.2. Conflict of interest

We declare that we have no conflicts of interest.

7.3. Funding and support

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7.4. Authors' contribution

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

7.5. Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

7.6. Using artificial intelligence chatbots

None.

References

1. Joseph H, Stancliff S, Langrod J. Methadone maintenance treatment (MMT): a review of historical and clinical issues. Mt Sinai J Med. 2000;67(5-6):347-64.
2. Clausen T, Anchersen K, Waal H. Mortality prior to, during and after opioid maintenance treatment (OMT): a national prospective cross-registry study. Drug Alcohol Depend. 2008;94(1-3):151-7.
3. Bell J, Zador D. A risk-benefit analysis of methadone maintenance treatment. Drug Saf. 2000;22(3):179-90.
4. Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. Addiction. 1998;93(4):515-32.
5. Glaizal M, Gazin V, Aymard I, Messina-Gourlot C, Richard N, Mallaret M, et al. Suicidal poisonings with methadone in France: Results of a two year national survey by the Toxicovigilance Network. J Clin Toxicol. 2012;50(9):841-6.
6. Gheshlaghi F, Izadi-Mood N, Mardani A, Piri-Ardekani MR. Dose-dependent effects of methadone on QT interval in patients under methadone maintenance treatment. Asia Pac J Med Toxicol. 2013;2(1):6-9.
7. Aghabiklooei A, Shadnia S, Hassanian-Moghaddam H, Zamani N. Acute respiratory distress syndrome caused by methadone syrup. Arh Hig Rada Toksikol. 2013;64(3):439-42.
8. Hoffman RS, Howland MA, Lewin NA, Nelson LS, Goldfrank LR. Goldfrank's Toxicologic Emergencies. 10th ed: McGraw Hill LLC; 2014. p. 329-33.
9. Walley AY, Doe-Simkins M, Quinn E, Pierce C, Xuan Z, Ozonoff A. Opioid overdose prevention with intranasal naloxone among people who take methadone. J Subst Abuse Treat. 2013;44(2):241-7.
10. Coffin PO, Sullivan SD. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. Ann Intern Med. 2013;158(1):1-9.
11. Shaw LV, Moe J, Purssell R, Buxton JA, Godwin J, Doyle-Waters MM, et al. Naloxone interventions in opioid overdoses: a systematic review protocol. Syst Rev. 2019;8(1):1-9.
12. Nath S, Tripathi M, Pandey C, Rao B. Naloxone-induced pulmonary edema: a potential cause of postoperative morbidity in laparoscopic donor nephrectomy. Indian J Med Sci. 2009;63(2):72.
13. Kim HK, Nelson LS. Reducing the harm of opioid overdose with the safe use of naloxone: a pharmacologic review. Expert Opin Drug Saf. 2015;14(7):1137-46.
14. Buajordet I, Næss A-C, Jacobsen D, Brørs O. Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. Eur J Emerg Med. 2004;11(1):19-23.

15. Sivilotti ML. Flumazenil, naloxone and the 'coma cocktail'. Br J Clin Pharmacol. 2016;81(3):428-36.
16. Brown R, Kraus C, Fleming M, Reddy S. Methadone: applied pharmacology and use as adjunctive treatment in chronic pain. Postgrad Med J. 2004;80(949):654-9.
17. Inturrisi C. Pharmacology of methadone and its isomers. Minerva Anestesiol. 2005;71(7/8):435.
18. Solhi H, Salehi B, Alimoradian A, Pazouki S, Taghizadeh M, Saleh AM, et al. Beneficial effects of Rosmarinus officinalis for treatment of opium withdrawal syndrome during addiction treatment programs: a clinical trial. Addict Health. 2013;5(3-4):90.
19. Haghighi-Morad M, Naseri Z, Jamshidi N, Hassanian-Moghaddam H, Zamani N, Ahmad-Molaei L. Methadone-induced encephalopathy: a case series and literature review. BMC Med Imaging. 2020;20(1):1-9.
20. Salgado R, Jorens P, Baar I, Cras P, Hans G, Parizel P. Methadone-induced toxic leukoencephalopathy: MR imaging and MR proton spectroscopy findings. AJNR Am J Neuroradiol. 2010;31(3):565-6.
21. Cerase A, Leonini S, Bellini M, Chianese G, Venturi C. Methadone-Induced Toxic Leukoencephalopathy: Diagnosis and Follow-up by Magnetic Resonance Imaging Including Diffusion-Weighted Imaging and Apparent Diffusion Coefficient Maps. JON. 2011;21(3):283-6.
22. Rando J, Szari S, Kumar G, Lingadevaru H. Methadone overdose causing acute cerebellitis and multi-organ damage. Am J Emerg Med. 2015;34(2):343. e1-3.
23. Hanna V, Senderovich H. Methadone in pain management: a systematic review. J Pain. 2021;22(3):233-45.
24. Clarke SF, Dargan PI, Jones AL. Naloxone in opioid poisoning: walking the tightrope. EMJ. 2005;22(9):612-6.
25. Clarke S, Dargan P. Intravenous bolus or infusion of naloxone in opioid overdose. EMJ. 2002;19(3):249-50.
26. McDonald R, Lorch U, Woodward J, Bosse B, Dooner H, Mundin G, et al. Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study. Addiction. 2018;113(3):484-93.
27. Williams K, Lang ES, Panchal AR, Gasper JJ, Taillac P, Gouda J, et al. Evidence-based guidelines for EMS administration of naloxone. Prehosp Emerg Care. 2019;23(6):749-63.
28. Clemency BM, Eggleston W, Shaw EW, Cheung M, Pokoj NS, Manka MA, et al. Hospital Observation Upon Reversal (HOUR) with naloxone: a prospective clinical prediction rule validation study. Acad Emerg Med. 2019;26(1):7-15.
29. Lewter LA, Johnson MC, Treat AC, Kassick AJ, Averick S, Kolber BJ. Slow-sustained delivery of naloxone reduces typical naloxone-induced precipitated opioid withdrawal effects in male morphine-dependent mice. J Neurosci Res. 2022;100(1):339-52.
30. Rzasa Lynn R, Galinkin J. Naloxone dosage for opioid reversal: current evidence and clinical implications. Ther Adv Drug Saf. 2018;9(1):63-88.
31. Yazdanbakhsh A, Kazemifar M. Comparison of Effects and Side Effects of Two Naloxone-Based Regimens in Treatment of Methadone Overdose. IJT. 2016;10(1):49-52.
32. Khosravi N, Zamani N, Hassanian-Moghaddam H, Ostadi A, Rahimi M, Kabir A. Comparison of Two Naloxone Regimens in Opioid-dependent Methadone-overdosed Patients: A Clinical Trial Study. Curr Clin Pharmacol. 2017;12(4):259-65.