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Original Article

Evaluating the incidence of syncope and electrocardiogram changes in methadone-treated volunteers quitting addiction in yazd

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Abstract

Objectives: Methadone is a synthetic opioid with a high affinity for opioid receptors, widely used as an effective intervention for opioid dependence and the management of acute and chronic pain. However, its use has been associated with serious cardiac side effects, including torsades de pointes (TdP) and prolonged QTc intervals. This study investigated the incidence of syncope and electrocardiogram (ECG) changes in individuals who underwent methadone treatment for addiction.

Methods: This cross-sectional study, conducted in Yazd in 2020, involved 100 participants seeking methadone treatment at an addiction clinic. A cardiologist recorded initial ECGs using a 12-lead ECG device, assessing parameters such as heart rhythm, QTc interval, and premature contractions. Participants were informed about the study procedures and the necessity of follow-up ECGs one week and three months after starting methadone. The researchers monitored the patients for three months with regular outpatient visits.

Results: The findings revealed a significant difference in syncope incidence based on ECG rhythm on day seven and month three, with higher rates observed in patients exhibiting junctional rhythms or PVC (p-value=0.000). Additionally, a significant relationship was found between syncope frequency and U wave status at month three (p-value=0.046).No significant associations were noted for ST segment changes or T wave variations. Furthermore, higher methadone doses, longer QTc intervals on day seven, and prolonged PR intervals correlated with increased syncope occurrences.

Conclusions: This study indicates that ECG-related variables and methadone dosage significantly influence syncope incidence among treated patients. Specifically, individuals with junctional rhythms or PVC and those receiving higher doses of methadone were at greater risk for syncope. Monitoring PR and QTc intervals is crucial for preventing syncope in patients undergoing methadone treatment.

Keywords: Methadone, Syncope, Electrocardiography, Opioid-Related Disorders, Iran

Introduction

Methadone, commercially known as Dolophine, is a powerful opioid analgesic utilized in the maintenance therapy for opioid addiction and the management of severe pain (1). Its efficacy stems from its agonistic action on mμ-opioid receptors (MOR) and antagonistic effects on N-methyl-D-aspartate (NMDA) receptors, offering a unique pharmacological profile that may confer a lower tolerance development compared to other opioids (2-5). As a maintenance option, Methadone Maintenance Therapy (MMT) is a safe, non-sedating, and potentially lifelong outpatient regimen with doses

that are carefully escalated to meet individual needs (6-8). Despite its therapeutic benefits, long-term methadone use can lead to a spectrum of adverse effects, including hormonal imbalances, gastrointestinal disturbances, neuropsychiatric symptoms, and dependence, with syncope being a particularly severe risk due to its association with reduced cerebral perfusion (9-12). Several studies have investigated methadone's clinical outcomes, highlighting its pharmacokinetics, characterized by high bioavailability and a variable half-life influenced by patient-specific factors. This has underpinned its widespread adoption in substance use disorder treatments, with significant increases in global patient numbers over recent years (9, 10, 13). Methadone distribution has been strictly regulated for maintenance in Iran since 2009, with a notable expansion of dispensing centers (3). While methadone's analgesic properties are beneficial for severe chronic pain management, its use carries inherent risks, including thermal dysregulation, orthostatic hypotension, and severe respiratory complications (14, 15). Moreover, the drug's narrow therapeutic index is linked to cardiac toxicity, with overdose-related sudden deaths being a grave concern (16). Cardiac complications such as QTc interval prolongation and Torsades de Pointes (TdP), a life-threatening variant of ventricular tachycardia, are particularly worrisome, with methadone-induced syncope indicating a potential reduction in cerebral blood flow (6, 14, 16, 17). Previous research has suggested that QTc prolongation is not consistently predictive of TdP occurrence, yet the associated risks necessitate careful monitoring (18, 19). Current debates revolve around the need for routine ECG monitoring, especially given the amplified risk of QT prolongation with higher methadone dosages and the influence of additional risk factors like concurrent QT-prolonging drugs and genetic predispositions (20-22). This study aimed to investigate the incidence of syncope and electrocardiogram (ECG) alterations among methadone-treated individuals in Yazd.

Materials and Methods

Study Design and Participants

This cross-sectional study was conducted in Yazd, Iran, targeting individuals undertaking addiction cessation. The recruitment period was from March 21, 2020, to March 20, 2021.Convenience sampling was employed to enroll participants until the desired sample size was reached. Using the following formula, the sample size was calculated at 80 participants, determined based on a 5% significance level and an 80% power of the test, informed by a standard deviation of 0.02 and a mean difference of 0.6 from previous research, which necessitated 88 subjects; however, accounting for a potential 12% attrition rate, 100 participants were selected.

$$N = \frac{\left(z_{\frac{\alpha}{2}} + z\beta\right) s^2}{(\bar{x}_1 - \bar{x}_2)^2}$$

Inclusion and Exclusion Criteria

Participants were selected from the Yazd population seeking to discontinue opioid use in 2020. Inclusion criteria were adults aged 18 years or older with documented opioid dependency. Researchers implemented the exclusion criteria to protect participant safety and data validity, excluding individuals with pre-existing abnormalities in baseline ECGs, diagnosed cardiac or pulmonary diseases, ongoing narcotic or morphine derivative usage, pregnancy or lactation, pacemaker implants, stroke history, significant anemia, seizure disorders, or those on QT interval-affecting medications, psychotropic drugs, or specific cardiac medications.

Ethical Considerations

The research was conducted according to ethical standards, paralleling the ethical considerations outlined in similar studies. Participants were informed about the study's aims and procedures. Individuals were enrolled in the study only after providing informed consent. All personal data were exclusively used for the purpose of this research and were maintained in strict confidentiality. Ethical approval for this study was obtained from the Shahid Sadoughi University of Medical Sciences in Yazd, with the assigned ethical code: IR.SSU.MEDICINE.REC.1399.197.

Data Collection

The data collection process began with the recruitment of 100 volunteers undergoing MMT for opioid addiction, selected via convenience sampling across multiple addiction treatment centers. The researchers applied inclusion criteria thoroughly to ensure the study's relevance and integrity. After providing

comprehensive informed consent, participants were asked to share a range of data, including demographic information, substance abuse history, and syncope episodes, focusing on cardiovascular health. Strict adherence to exclusion criteria ensures that participants in a study are selected based on well-defined guidelines. A detailed checklist was completed for each participant after explaining the study protocol documenting demographic information, health conditions, treatment plans, and current medications. Baseline ECGs were performed using a standard 12-lead ECG machine, operated by a qualified cardiologist. Participants were queried about syncope episodes, defined as sudden, brief losses of consciousness not attributable to preceding drug administration. ECGs were recorded before the daily methadone dose and analyzed at a standard speed of 25 mm per second. A cardiologist meticulously reviewed all ECG outputs, focusing on parameters such as heart rate, rhythm abnormalities, QTc interval, ST segment alterations, T wave features, QRS complex dimensions, PR interval, coupling intervals, and the presence of PVCs (Premature Ventricular Contractions), PACs (Premature Atrial Contractions), and U waves. Participants began methadone treatment with a prescribed dose and were informed about the necessity of follow-up ECGs at one week and three months into treatment. Monitoring continued over three months, with daily clinic visits for methadone administration. Follow-up ECGs were conducted at the predetermined intervals with the same equipment and cardiologist to ensure consistency. This approach facilitated a longitudinal comparative analysis to evaluate trends in syncope incidence and ECG parameter alterations.

Statistical Analysis

Data were carefully collected, coded, and entered into a computerized database for analysis.Statistical analysis was conducted using SPSS software, version 25. Descriptive statistics, including means (SD), frequencies, and percentages, were employed to summarize the data. To analyze the continuous variables, the independent Samples t-test and Paired Samples t-test were utilized. The Mann-Whitney U test was applied for distributions that did not follow a normal distribution. The Chi-square test was used to analyze categorical variables. The p-value of less than 0.05 was considered statistically significant across all tests.

Results

Participant Demographics

The average age of participants was 45.81 ± 13.15 years, with a minimum age of 20 and a maximum age of 72. Out of the 100 patients, 78 were treated with liquid methadone, while 22 received methadone tablets. Table 1 shows average values for various variables, methadone dosage, duration of methadone use, baseline heart rate (HR), baseline QTc interval, and baseline PR interval.

ECG Rhythm Distribution

Table 1 shows the distribution of ECG rhythms at baseline, on the seventh day, and on the third month.

Table1. ECG Rhythm Distribution on Day 0, Day 7, and Month 3

Time	Rhythm Type	Frequency - Percentage
Day Zero	Sinus	100%
Day Seven	Sinus	65%
	Atrial PAC	11%
	Junctional	9%
	Ventricular PVC	15%
Month Three	Sinus	65%
	Atrial PAC	11%
	Junctional	9%
	Ventricular PVC	15%

Syncope Frequency Distribution

Table 2 illustrates the results regarding syncope frequency based on methadone form. The analysis using Chi-Square tests indicated no statistically significant difference in syncope frequency based on methadone form. (P-value = 0.533).

Table2. Distribution of Syncope According to Methadone Form

Syncope	Methadone Form		P-value
	Syrup	Tablet	
With Syncope	23 (29.5%)	5 (22.7%)	0.533
Without Syncope	55 (70.5%)	17 (77.3%)	

Furthermore, syncope frequency based on ECG rhythm on the seventh day showed a statistically significant difference (P-value = 0.000), indicating a higher likelihood of syncope among patients with junctional or PVC rhythms.

Table3. Syncope Distribution by ECG Rhythm on Day 7

		Syncope		P-Value
		With Syncope	Without Syncope	
ECG rhythm on the seventh day	Sinus (percentage)	13 (20%)	52 (80%)	0.000
	Atrial (PAC) (percentage)	1 (9.1%)	10 (90.9%)	
	Junctional (percentage)	2 (22.2%)	7 (77.8%)	
	Ventricular (PVC) (percentage)	12 (80%)	3 (20)	

Correlation of Variables with Syncope

Table 4 illustrates the average values of various study variables based on syncope status. T-test analysis indicated significant differences in methadone dosage, baseline PR interval, and QTc interval on Day 7.

Table4. Average Variables Based on Syncope Status

Variable	Syncope Status		P-value	Total
	With Syncope (Mean±SD) N=4,023.35	Without Syncope (Mean±SD) N=2,695.67		Mean±SD
Methadone Dose (mg)	100±8.71	64.24±14.47	0.00	74.25±20.77
Duration of Methadone (days)	1785.89±718.68	820.69±747.25	0.65	1090.95±855
Baseline QTc Interval	410.39±18.56	396.93±16.52	0.30	400.70±18.07
QTc Interval Day 7	462.46±31.45	421.15±21.51	0.00	439.92±28.31
QTc Interval Month Three	458.89±22.90	434.10±28.17	0.17	441.04±28.94
Baseline HR	73.93±7.37	69.10±6.67	0.16	70.45±7.18
HR Day 7	63.93±5.83	63.13±4.70	0.06	63.35±5.02
HR Month Three	55.36±4.89	57.43±5.43	0.36	56.85±5.34
Baseline PR Interval	152.86±21.91	158.75±17.59	0.04	157.10±18.97
PR Interval Day 7	211.43±14.06	189.17±15.17	0.12	195.40±18.79
PR Interval Month Three	248.21±15.16	212.15±15.74	0.42	222.25±22.47

Discussion

Methadone, a potent μ-opioid receptor agonist, is metabolized in the liver via demethylation by cytochrome P450 isoenzymes, including CYP3A4, CYP2B6, and CYP2C19, and its metabolites are excreted in urine (9, 10). The therapeutic dose of methadone is dangerously close to its lethal dose, and misuse can lead to fatal cardiac events (15). Cardiotoxic effects, such as QTc interval prolongation

and TdP, a life-threatening arrhythmia, are particularly concerning (16, 17). TdP can result in palpitations, dizziness, and syncope (23). Our study assessed the incidence of syncope and ECG changes in volunteers discontinuing methadone. We found significant increases in the mean QTc interval from baseline to day seven and month three (400.75 ms, 439.92 ms, and 441.04 ms, respectively), indicating a consistent rise post-methadone administration. Similar findings have been documented in the literature, with studies reporting QTc interval prolongation in methadone-treated patients (22, 24-27). Our research also identified factors contributing to syncope in methadone-treated patients, including ECG rhythm, U wave status, methadone dosage, and QTc and PR intervals. Notably, patients with abnormal rhythms, absent U waves, higher methadone doses, prolonged QTc intervals, and shorter baseline PR intervals had higher syncope rates. Studies corroborate these findings, suggesting a dose-dependent risk of syncope with methadone (28).While some studies have found correlations between methadone dose and QTc interval prolongation (25, 26), we did not observe a significant link between the duration of methadone use and syncope incidence. However, our findings do not show a significant relationship between patient age and syncope frequency, contrasting with some studies that indicate older age and higher doses correlate with increased QTc intervals (27). This study benefits from a detailed longitudinal design with consistent ECG monitoring at multiple intervals (baseline, day seven, and month three). The rigorous application of inclusion and exclusion criteria ensured participant homogeneity, enhancing the reliability of our findings. Additionally, the standardized ECG evaluations conducted by a single cardiologist reduced inter-observer variability. However, several limitations should be acknowledged: First, convenience sampling and reliance on volunteer participants may limit the generalizability of findings. Second, information on substance use history and syncope episodes was self-reported, potentially introducing recall bias. Third, Due to the study's cross-sectional design, causal relationships between methadone use and ECG changes or syncope could not be definitively established. Fourth, although calculated with a safety margin, the sample size may limit the power to detect less frequent cardiac events. Our findings highlight the critical need for regular ECG monitoring in methadone-treated patients, particularly during the early stages of therapy. We recommend monthly ECG assessments to detect cardiac abnormalities, with timely cardiology referrals in cases of significant rhythm disturbances or QTc prolongation. Moreover, given the observed dose-dependent risk, strategies to reduce methadone dosage or substitute it with alternative therapies should be explored to mitigate cardiac risks.

Conclusion

This study identified key factors influencing the incidence of syncope in patients undergoing methadone treatment, including higher methadone doses, prolonged QTc and PR intervals, and specific ECG rhythms (junctional and PVC). These findings highlight the importance of regular ECG monitoring, especially in the early stages of treatment, to promptly detect and manage cardiac abnormalities. Dose adjustments and careful evaluation of high-risk patients can significantly reduce syncope risk, enhancing patient safety during methadone therapy.

Ethical Statements

This study was conducted according to the ethical principles, outlined in the Declaration of Helsinki. Ethical approval was obtained from the Shahid Sadoughi University of Medical Sciences in Yazd (Ethics Code: IR.SSU.MEDICINE.REC.1399.197). Informed consent was obtained from all participants before enrollment, and their data were kept confidential and used solely for research purposes.

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Authors' Contributions

Hesam Hosseini: Conceptualization, study design, data analysis, manuscript drafting, and final approval.
Mehdi AmirHeydary: Supervision, critical review of the manuscript, and final approval.
Seyed mostafa Seyedhosseini: Data acquisition, interpretation of findings, and manuscript revision.
Mohammad Poorebrahimi: Methodology support, clinical expertise, and manuscript editing.
Mohammadtaghi Sarebanhassanabadi: Statistical analysis, data interpretation, and manuscript preparation.
All authors have read and approved the final version of the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest related to this study.

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