

# Relationship between Corrected-QT Intervals and Other ECG Characteristics with Methadone Dose in Methadone Maintenance Treatment (MMT) Patients and Healthy Subjects: A Case- Control Study

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## Abstract

**Background:** In this study we assessed the relationship between corrected-QT intervals and other ECG characteristics with methadone dose and other parameters in MMT patients and healthy subjects.

**Methods:** This was a case-control study which was carried out on patients underwent MMT and healthy control group who had been referred to Ebne-Sina academic hospital, Mashhad during 2014 - 2015. At the time of the study, 40 patients who received MMT therapy for at least 6 months and 40 voluntary healthy subjects who matched on age and sex enrolled in the study. 12-lead ECG was performed for all the patients. Mean QT interval, PR interval and QRS duration in every 12 leads were documented for each patient in maximum.

**Results:** To evaluate the patients, we divided 80 patients into two groups: 40 patients under treatment with Methadone and 40 voluntary participants as control group. There were 20 males and 20 females in each group. Duration of addiction was  $214.80 \pm 126.99$  months in MMT group. Significant differences were observed in PRi between the patient and control groups ( $P = 0.007$ ), and also between methadone dose and PRi ( $r = 0.468$ ,  $P = 0.038$ ) in males. QTc prolongation was reported in 4 patients of addicted group (10%). All of the QTc prolongation patients were female ( $P = 0.037$ ). There was significant relationship between PRi and weight ( $P = 0.015$ ), addiction period ( $P = 0.011$ ), methadone treatment period ( $P = 0.018$ ) as well as methadone dosage ( $P = 0.14$ ). Methadone cut off point of 65 mg had a significant relationship with systolic blood pressure ( $P = 0.002$ ), diastolic blood pressure ( $P = 0.013$ ), QTci ( $P = 0.016$ ) and QRS ( $P = 0.044$ ); however, no significant relationship was reported with PRi ( $P = 0.451$ ).

**Conclusions:** We found that there is no exact dosage of methadone in which the side effects such as TdP (Torsade de pointes) or QTc prolongation can be predicted. Female gender and methadone dosage  $\geq 65$  mg were risk factors of our study for QTc prolongation which may result in subsequent deteriorated conditions.

**Keywords:** Electrocardiographic Indexes, Maintenance Methadone Therapy, Corrected QT-Interval, Addiction

## 1. Background

Methadone is a synthetic long-acting analgesic agent that has central performance with high affinity for  $\mu$  receptors. It is used to treat opioid dependence named Methadone maintenance therapy (MMT) (1). It can reduce the risk of mortality caused by substance overdose. However, due to the fatal and life-threatening effects, methadone complications should be considered carefully (2). Its common adverse consequences include nausea, constipation, sleepiness, itching and respiratory dysfunction. Other uncommon adverse effects are headache, muscle spasm, cardiovascular instability, urinary retention, low gastrointestinal motility and myoclonic jerking (3). QT

interval prolongation in ECG (4-9), increased QT dispersion (9), prolongation of QRS duration (10, 11) and PR interval (11), torsade de pointes tachycardia (12, 13) are some of the cardiac side effects of using methadone. The relationship between the electrocardiographic indexed findings and methadone therapy is nearly well known. Many studies have evaluated the relation between high dose methadone and a prolonged QT interval and torsade (14). It is related to QT interval prolongation and progression to torsade de pointes independently. Laboratory studies have shown that methadone has different effects on cardiac performance (15). It lowers maximum rate of depolarization and increases potential duration in Purkinje fibers. These results can elongate the QT or QTc interval (14). Experimen-

tal evidence has shown that methadone has multiple effects on cardiac function (15). It decreases maximum rate of depolarization and increases action potential duration in Purkinje fibers (14).

Oral opioids are the main choice drug of chronic pain therapy (16). Methadone has attracted an increasing interest in palliative care (17). Comparison of methadone therapy in healthy subjects and addicted patients has not yet been evaluated in Iranian population. In this study we assessed the relationship between corrected-QT intervals and other ECG characteristics with methadone dose and other parameters in MMT patients and healthy subjects.

## 2. Methods

This was a case-control study which was performed on patients underwent MMT and healthy control group who had been referred to Ebne-Sina academic hospital, Mashhad during 2014 - 2015.

### 2.1. Subjects

At the time of the study, 40 patients who received MMT therapy (case group) for at least 6 months and 40 voluntary healthy subjects (control group) who matched on age and sex enrolled in the study.

### 2.2. Inclusion and Exclusion Criteria

The patients addicted to methadone with the history of consumption for at least 6 months, were included in the study. The exclusion criteria were: pregnancy, using drugs such as Tamoxifen, Letresol, all types of androgenic drugs like Nandrolone, oral contraceptive drugs, hypothyroidism or hyperthyroidism drugs like Levothyroxine, liothyronine, Methimazole, prolactin-affecting drugs like Bromocriptine and Cabergoline, drugs affected electrocardiogram (ECG) indexed like antidepressant, antipsychotic, Lithium, Benzodiazepines, anticonvulsants, Lidocaine, Amiodarone, Verapamil, Digoxin, Beta-blockers, Adenosine, specific chemotherapy drugs like Adriamycin or others. Other exclusion criteria were acromegaly, nephrotic syndrome, history of gonadotropin-related disorders or previous hyperprolactinemia, patients with congenital Long QTc syndromes, patients who had artificial pacemaker, patients under treatment with methadone less than 6 months.

### 2.3. Electrocardiography

We performed a 12-lead electrocardiogram at 50 mm/second to measure the QT interval. 3 consecutive sinus beats of QT intervals were measured manually with means of a caliper in each of the 12 leads. End of the T

waves was reliably identified, and a mean QT interval for every lead was computed. QT prolongation was defined based on the American College of Cardiology (ACC): QTc more than 460 ms for women and more than 450 ms for men.

### 2.4. Echocardiographic Indexes

Mean QT Interval, PR Interval and QRS Duration in every 12 leads were documented for each patient in maximum. Measurements were made by an observer who was not aware of the patients' characteristics. The QT corrected for RR (QTc) was computed using Bazett's formula,  $QTc = QT/\sqrt{RR}$  (18).

### 2.5. Analysis and Assays

For each patient we drew up a checklist of demographic and medical data including Methadone dose, age, gender, body mass index (BMI), blood pressure, duration of Methadone use, duration of addiction, values of hormone tests and ECG indexes.

### 2.6. Ethics

We obtained informed consent from the patients. This study was verified by the Ethics Committee of Mashhad University of Medical Sciences.

### 2.7. Statistical Analysis

Data were statistically analyzed using SPSS software (Version 21, Chicago, IL, USA). Data were then presented as mean  $\pm$  SD in each group. Kolmogorov-Smirnov test was used to determine normal distribution of the variables. Independent sample t-test was used in quantitative variables and chi-square test for qualitative ones. Mann-Whitney Test was also used in non-parametric characteristics. P Value < 0.05 was considered as significant.

## 3. Results

### 3.1. Demographic and Basic Data

There were 20 males and 20 females in each group. Duration of addiction was  $214.80 \pm 126.99$  months in MMT group. Mean weight of MMT group was  $71.80 \pm 12.33$  vs healthy group with  $71.22 \pm 11.57$  kg. Mean time of Methadone consumption was  $58.10 \pm 28.60$  months. Mean dosage of Methadone used in MMT group was  $59.00 \pm 19.45 \pm 28.60$  mg/day. Other demographic data is shown in Table 1.

**Table 1.** Demographic and Medical Data of Participants<sup>a</sup>

Characteristics	Methadone Group	Control Group	P Value
Age, y	48.13 ± 9.88	45.78 ± 10.95	0.305
BMI, kg/m <sup>2</sup>	27.39 ± 5.49	24.50 ± 3.82	0.012
SBP, mmHg	115.68 ± 17.65	120.63 ± 12.41	0.279
DBP, mmHg	77.00 ± 12.08	78.18 ± 6.50	0.737
Duration of Methadone use, mo	214.80 ± 126.99	-	-

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

<sup>a</sup>Values are expressed as mean ± SD.

### 3.2. Electrocardiogram Characteristics

We summarized ECG evaluated factors in Table 2. Totally, QTcI was significantly higher in Methadone users compared with control groups ( $P = 0.045$ ) based on Mann Withney test. Significant differences were obtained in PRi between the patients and control groups ( $P = 0.007$ ). We showed a meaningful relationship between dose of Methadone and PRi ( $r = 0.468$ ,  $P = 0.038$ ) in males. There was no significant difference in QRS duration between Methadone users and control groups ( $P = 0.419$ ). QTc prolongation was reported in 4 patients of addicted group (10%). All of QTc prolongation patients were female ( $P = 0.037$ ). None of the variables could predict QTc prolongation in addicted patients except gender ( $P = 0.036$ ). QRS widening was seen in three cases in addicted patients (7.5%). None of the variables could predict QTcI in addicted patients. There was no significant correlation between QTc prolongation and Methadone dose and addiction period ( $P > 0.05$ ) (based on Independent t-test); however, there was a significant correlation between QTc prolongation and period of Methadone treatment period ( $P = 0.016$ ). QRS widening was significantly related with heart rate ( $P = 0.008$ ) in addicted patients. QRS widening was also significant in female addicted patients ( $P = 0.039$ ).

## 4. Discussion

Methadone replacement therapy program is developing in Iran, and its dangerous complications in the addict subjects have been reported progressively (2). Because of the growing number of methadone maintenance treatment centers in recent decades, acute methadone overdosing has been changed into one of the most poisoning substances in Iran (19). MMT was initiated in Iran in 2003 and developed gradually and now there are more than 1500 active MMT centers in Iran (20). In this study we evaluated the pattern of methadone usage in addicted patients and

compared their ECG characteristics with the healthy volunteers. To our knowledge, there are rare comparisons of ECG variables between addicted and healthy subjects till now in Iran.

We showed that there was no significant correlation between QTcI and methadone treatment period, methadone dosage and addiction period ( $P > 0.05$ ), and QTcI was significantly more in methadone group comparing to control group ( $P = 0.045$ ). We also showed that there was a significant relationship between methadone cut off point of 65 mg and systolic blood pressure ( $P = 0.002$ ), diastolic blood pressure ( $P = 0.013$ ), QTcI ( $P = 0.016$ ) and QRS ( $P = 0.044$ ), but no relationship was reported with PRi ( $P = 0.451$ ). We showed that methadone dosage and female gender could be regarded as predictor for QTcI prolongation. Methadone dose is a main risk factor for QTc prolongation (21, 22). Roden compiled a list of factors that may increase the patient's potential development of Q-T interval prolongation and subsequent progression to Torsade de Point (TdP), including female sex, hypokalemia, previous cardiac disorders, congenital long Q-T syndrome (LQTS), tendency to DNA polymorphisms and a history of drug interference. If these risk factors have not been studied in the patients receiving methadone, they should be taken into consideration while treatment (23). Similar to our results, Krantz et al. showed that methadone dose in a day can predict the QTc interval ( $r = +0.51$ ,  $P = 0.03$ ) and other factors evaluated, including age, gender, hypokalemia or structural heart disease, and presence of QT-prolonging drugs cannot not be used as predictor of the QTc interval (22). Kornick et al. (21) showed a significant and nearly linear linkage between QTc values and log-dose of methadone ( $P < 0.0001$ ). In another study, female sex, medications interfering, hypomagnesemia, structural cardiac disorder and hypokalemia were considered as the risk factors for QTc prolongation and TdP (24). Cruciani et al. (25) showed that 33% had QTc prolongation (males 40%, females 20%;  $P = 0.03$ ) and a marked dose response was obtained in males on methadone < 12 months ( $r = 0.60$ ,  $P = 0.02$ ). They also suggested that methadone may prolong the QTc interval in specific subpopulations but it poses little risk of serious prolongation. Peles et al. in contrast to our results showed that dose of methadone and its serum levels did not link with QTc (26). Maremmanni et al. (27) assessed abnormal QTc interval in 83 heroin addicts who underwent long-term MMT and received methadone dosages between 10 - 600 mg/day. Nearly, 83 % of them had QT prolongation more than the reference values. No correlation was observed between QT prolongation and methadone dosage. Huh and Park (28) evaluated 130 patients: 90 patients in the methadone group and 40 patients in the control group. QTc interval was markedly longer in the methadone group.

**Table 2.** Comparison of EKG Evaluated Factors in Both Groups<sup>a</sup>

Characteristics		Methadone Group	Control Group	P Value
QTcI, ms	Male	430.00 ± 54.29	409.50 ± 15.64	0.187
	Female	481.50 ± 62.17	443.00 ± 13.41	0.120
	Total	455.75 ± 63.24	426.25 ± 22.24	0.046
PRi, ms	Male	129.00 ± 38.64	167.50 ± 19.70	0.001
	Female	149.00 ± 31.42	149.00 ± 25.73	0.956
	Total	139.00 ± 36.22	158.25 ± 24.48	0.007
QRS, ms	Total	82.00 ± 18.01	80.00 ± 0.00	0.419

Abbreviations: ms, millisecond; PRi, P-R interval; QRS, QRS duration; QTcI, corrected QT interval.

<sup>a</sup>Values are expressed as mean ± SD.

QTc interval was not associated with methadone dose ( $P = 0.9$ ) and serum concentration or duration of treatment. Fareed et al. (6) confirmed in their study that methadone dose may be related to QTc prolongation. They specified 3 risk factors for marked QTc prolongation in patients undergoing MMT, including recent cocaine use, uncontrolled blood glucose and CHF. Reddy et al. (29) showed no association between QTc prolongation and methadone dose, and they explained it by the relatively low dose of methadone in their cohort. QTc prolongation risk is correlated with methadone dose and it has important practical points in regard to the need of ECG monitoring before and during the methadone treatment (30). For QTc prolongation in methadone users, regular visits, screening and monitoring of all patients started on methadone are recommended (31). Female gender patients who underwent MMT therapy should be carefully followed up as high risk patients in order to prevent other comorbidities.

We showed that QRS duration had no relation with methadone treatment period, methadone dosage and addiction period and other clinical and demographic variables ( $P > 0.05$ ). Also we showed that there was a correlation between PR interval and methadone dose and also a meaningful difference between control and methadone groups in males. Schmittner et al. (32) showed no meaningful alterations in mean heart rate, PR interval, QRS duration, or QTc interval after methadone administration, so a larger prospective study has shown that single methadone therapy elevates QTc interval modestly along with having no effect on QRS duration (33). Our results of PR interval changes in methadone users are a new finding for this drug and it requires to be investigated by other studies. Our study limitations were low sample size and short-term follow-up period.

#### 4.1. Conclusions

In this study we showed that methadone dosage and female gender could predict the QTc prolongation in patients underwent MMT. We also showed that methadone dose was significantly correlated with PRi. Another finding of our study was report of 4 patients with QTc prolongation in subjects with low-dose methadone treatment. This showed that there is no exact dosage of methadone in which the side effects such as TdP or QTc prolongation can be predicted. We found that 65mg methadone cut off point is related to QTc prolongation and QRS widening in addicted patients. This was a case-control study in which we compared the results of ECG in healthy subjects and addicted patients. Female gender and methadone dosage more than 65mg were risk factors of our study for QTc prolongation that can make subsequent deteriorated conditions. We recommended performing this comparative study in large population, multi-centric and long-term cohort investigation in order to make a regional guideline based on the Iranian population study.

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#### Footnote

**Conflict of Interest:** All authors declare any competing interests.

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