Opium-associated QT Interval Prolongation: A Cross-sectional Comparative Study

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ABSTRACT

Background: Toxicity and side effects of long-term use of opioids are well studied, but little information exists regarding electrophysiological disturbances of opium consumption. While natural opium has been regarded safe to a great extent among traditional communities, concerns are emerging owing to the available evidence of QT prolongation that have been exposed during recent outcome surveillance of patients under opioid use. Potential QT prolonging interactions would raise a higher level of such concern in opium users during COVID pandemic and warrant attention.

Materials and methods: This study was designed to detect the prevalence of QTc prolongation among opium users and nonusers. Two groups were compared with regard to gender, age, and median QTc interval. Normal and prolonged QTc intervals of user group were compared with respect to age, sex, dose of opium consumption, and duration of opium consumption.

Results: 123 opium users and 39 controls were investigated. Median QTc interval in opium user and non-user group was 460 vs 386 milliseconds, respectively (p value < 0.001). In all, 59.3%, (95% CI: 50.51–67.62%) of cases and none of non-user had prolonged QTc interval (p value < 0.001). There was no significance between normal and prolonged QTc intervals with respect to dose and duration of opium use.

Conclusion: This study indicated that opium consumption is associated with QTc prolongation. This prolongation does not relate to dose and duration of opium use. Further study is propounded to assess the clinical significance of these results and to determine risk rating of opium compared to other opioids in this regard.

Keywords: Opioids, Opium, QT interval, QT prolongation.

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INTRODUCTION

Cultivation of opium poppy (*Papaver somniferum*) and production of raw opium have been intertwined with many cultures around the world.[1–7] The opium market serves both for producing the medicinal preparations such as morphine and codeine and securing the illicit trade of heroin and opium. The traditional belief of beneficial properties along with the analgesic effect of opium has turned into the rising trend of a tremendous illegal and adulterated opium use leading to health and economic calamity.[8,9] Nevertheless, opium pharmaceutical product in the form of opium tincture has been recently introduced to control opioid withdrawal and reduce addiction harms.[10–14]

The effect of opioids on cardiac electrical activity has been the matter of concern for physicians and pharmacists, since considering the arrhythmogenicity of a drug can weigh up the pros and cons of treatment or to prioritize the drug administration.[15] In particular, the usage of the varying sedatives in perioperative settings and administration of specific therapeutics for COVID-19 patients with possible QT prolonging interactions would raise a higher level of such concern in opium users and warrant attention and further investigation. Many studies have elaborated the adverse and protective effects of opium use on cardiovascular risk factors.[16–23] Meanwhile, little evidence has documented the association of opium use with cardiotoxicity and heart electrophysiology.[19] Morphine is the main direct derivative of opium and accounts for 8–17% of the quantitative alkaloid content in opium.[7] Morphine has been considered low risk from the perspective of QT interval prolongation[15] and has been suggested for treating opioid

addicts who have a prolonged QT interval.[24] However, opium is a mixture of several substances with different effects that may ensue the different clinical manifestations.[9] Yet, there is no evidence that opium consumption is associated with the higher prevalence of prolonged QT interval compared to non-user general population. Hence, we conducted this study to demonstrate whether there is association between opium use and prolongation of QT interval.

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MATERIALS AND METHODS

Study Design

The study population included consecutive admitted patients in the internal medicine ward of the Bu Ali University Hospital (Qazvin, Islamic Republic of Iran) between July 23, 2017, and August 22, 2017, who adhered to the selection criteria and provided written informed consent. The patients were seeking care for internal medicine problems other than cardiac or problems that may influence heart electrophysiology. The cases may have been taken diverse drugs for chronic illnesses. We excluded the patients who are taking drugs influencing cardiac electrophysiology. Inclusion criteria were admissions with diagnosis of noncardiac reasons and age of 18 years and older. All individuals who had history of coronary artery disease (CAD), family history of sudden death, advanced heart disease, concomitant use of drugs, and electrolyte imbalance potential to prolong QT interval were excluded from the study. The assumption was cigarette smoking does not influence QT interval and thus was not assessed in this study. The user group consisted of opium users and were defined as cases who have been using opium oral or smoking per day for at least 6 months. We used self-reporting opium use as a plausible means of detecting existing addictive habit.[25] This study has collected data on typical types of opiates used locally interchangeably—that is, teriak, shireh, and sukhteh. A non-user group was enrolled to a comparison group and included non-cardiac patients who have not been using opium and other addictive opioids and had been hospitalized at the same study period and conformed to exclusion criteria. Individuals were assessed by face-to-face interview and access to the medical record information. Medical history and necessary clinical and 12-lead electrocardiographic findings were recorded on a defined questionnaire and then entered into the defined database. Two groups were compared with regard to gender, age, and mean QTc interval. QTc was calculated using Bazett's formula.[25] We used 2005 European protocol for QTc assessment.[26] QTc value greater than 440 milliseconds (ms) in males and 460 milliseconds in females was defined as prolonged QTc.[26] Normal and prolonged QTc intervals of case group were compared with respect to dose and duration of opium consumption.

Ethical Issues

Informed consent was obtained from the patients, and confidentiality was preserved all over the study. Ethical issues were maintained with regard to the Helsinki Declaration 1975 as revised in 1983. The study was approved by the Ethical Committee of Research of Qazvin University of Medical Sciences.

Statistical Analysis

A sample size was calculated based on published data of two earlier studies in which QTc interval prolongation were significantly higher in opium user patients compared to non-user (60 vs 30%).[27,28] It was estimated that 162 patients were needed to detect a difference between prevalence of QTc interval prolongation within two groups, with a ratio of non-user to user of 0.3, power of 80%, and an α level of 0.05.

The data were analyzed by IBM SPSS 22 statistical package (SPSS Inc, Chicago, and IL, USA). Distributions of continuous data were assessed for normality using the Kolmogorove Smirnov test, and all were non-normal distributions. Hence, continuous variables were described as median (IQR: interquartile range) and were compared using nonparametric (Manne–Whitney U) test. Categorical variables were summarized as frequencies and percentages. We compared proportions using the Chi-square test or Fisher's exact test. To assess effect of opium dependency on QTc interval prolongation, we used a binary logistic regression model. Odds ratio (OR) with 95% confidence interval (CI) was reported. A p value of <0.05 was considered statistically significant, and all tests were two-tailed.

RESULTS

A total of 162 individuals were investigated for this study, including 123 opium users and 39 individuals not using opium who served as a non-user group.

Table 1 outlines characteristics of study participants and the pattern of opium consumption with respect to dose, duration, and route of opium use.

The median age in opium users was 42 years and in control was 39 years which was not statistically different (p value = 0.388). Among case and control patients, 54% were male and 46% were female. No significance was found while two groups were compared with respect to gender (p value = 0.278). Among opium users, daily dose of opium consumption ranged from 0.5 g/day to 12 g/day, and the duration of opium consumption ranged from 1 to 45 years. A combination of oral and smoking route of opium consumption was the most common method (44.7%), followed by smoking, and oral. The opium user and non-user groups were compared based on QTc length.

Table 2 details the median [IQR] of QTc intervals in user and non-user groups. The assessments showed that opium use was significantly associated with higher QTc intervals in comparison to non-user group ($p < 0.0001$). Out of 123 opium users, 73 (59.3%, 95% CI: 50.51–67.62%) had prolonged QTc interval. Accordingly, out of 39 control cases, all individuals had normal QTc. According to these findings, frequency of individuals with prolonged QTc intervals were significantly more common in opium user group compared to the control individuals (p value < 0.0001).

In binary logistic regression model (to assess effect of opium dependency on QTc interval prolongation) included variables were age, sex, daily dose, and duration of opium consumption as covariate. After an enter method analysis, sex and age remained in the model (male gender and older age as independent risk factors for prolonged QTc interval) (Table 3). Male gender and older age

Table 1: Demographic among participants and pattern of opium use in user group

Characteristic		Study group		
		Opium users	Non-users	p value
Age (years, median [IQR])		42 [35–51]	39 [29–57]	0.388[a]
Gender (no, %)	Male	69 (56.1%)	18 (46.2%)	0.278[b]
	Female	54 (43.9%)	21 (53.8%)	
Opium use duration (years, median [IQR])		10 [4.5–20]	N/A	N/A
Amount of daily opium use (g, median [IQR])		2 [2–4]	N/A	N/A
Route of opium use (no, %)	Oral	28 (22.8%)	N/A	N/A
	Smoking	40 (32.5%)	N/A	N/A
	Both	55 (44.7%)	N/A	N/A

IQR, interquartile range; QTc, the corrected QT interval; g, gram; N/A, not applicable
[a]Manne–Whitney U test; [b]Chi-square test

Table 2: QTc interval measures among opium users and non-users group

Characteristic		Study group*			
		Opium users	Non-users	Total	p value
QTc (ms, median [IQR])		460 [440–490]	386 [370–408]	—	<0.0001[a]
QTc (no, %)	Normal	50 (40.7%)	39 (100.0%)	89 (54.9%)	<0.0001[b]
	Prolonged	73 (59.3%)	0 (0.0%)	73 (45.1%)	

*ms, milliseconds, no. (%); IQR, interquartile range; QTc, the corrected QT interval
[a]Manne–Whitney *U* test; [b]Chi-square test

Table 3: Male sex and age were associated with a 3.68 and 1.04-fold increased risk of QTc prolongation in user group, respectively at step 2. Enter method, age, sex, daily dose and duration of opium consumption

Variable		β	SE	p	Exp (β)	95% CI for Exp (β) Range
Step 1[a]	Sex (male)	1.233	0.387	0.001	3.432	1.609–7.323
	Constant	−0.266	0.277	0.338	0.767	
Step 2[b]	Sex (male)	1.303	0.400	0.001	3.680	1.680–8.060
	Age	0.042	0.018	0.020	1.043	1.007–1.080
	Constant	−2.114	0.842	0.012	0.121	

*No. (%), QTc, the corrected QT interval; CI, confidence interval

were significant predictors of QTc prolongation (OR: 3.68, 95% CI: 1.680–8.060, *p* value = 0.001 and OR: 1.04, 95% CI: 1.007–1.080, *p* value = 0.020, respectively) in the user group.

DISCUSSION

The present study found that the QT interval is prolonged in 59.3% of opium users and none of non-opium users, and this difference was statistically meaningful.

When addicted patients are prepared for surgery or procedures requiring anesthesia, the usage of sedatives, particularly in the setting of acute pain management, can become a significant challenge. In these patients, drugs that may further prolong the QTc interval should be administered with care and with appropriate electrocardiogram (ECG) monitoring. Opium has been associated with QT prolongation; however, these patients may require to continue their maintenance dose during the perioperative period, and additional opioids may be used during surgery or for breakthrough pain in the postoperative period.[29] As a result, postoperative monitoring for QTc prolongation is essential.

Accordingly, addicted COVID-19 patients who are hospitalized and take some drugs (e.g., hydroxychloroquine, macrolide, quinolone, haloperidol, ondansetron, and amiodarone) can experience QTc prolongation and torsades de pointes (TdP) as an adverse drug event. There is a critical need for rigorous, large-scale studies and risk-benefit assessment prior to initiating COVID-19 therapeutics, with careful attention to medication interactions, cardiac manifestations, routine electrocardiograms, and electrolyte monitoring especially in opium-addicted patients.[30]

We could not find an association between dose and duration of opium consumption with QT interval prolongation. Several studies have investigated the effect of opium addiction on cardiovascular system.[31,32] Some of these studies reported harmful effects of opium on this system.[16,33] Along with the continuing advances in opioid therapies, our understanding about the cardiac effects of these opioids has increased over time. In particular, investigating potential effect of opioid agents in causing QT interval prolongation has been of great interest, as it may induce TdP and sudden death.[15] QT interval prolongation has been documented during

the administration of methadone,[34–36] buprenorphine,[34,37] levomethadyl,[34] oxycodone,[38] and tramadol.[39] Morphine is a less investigated opioid analgesic in this regard. We found three review articles that have tried to achieve a conclusive result in view of the impact of opioids on cardiac electrophysiology including QT interval prolongations.[9,15,40] In a cross-sectional study conducted by Fanoe et al., no association between morphine and QT was observed.[38] In the more recent study conducted by Tung et al., the effects of methadone and morphine were assessed and compared the effects of methadone and morphine on the heart rate, mean arterial pressure, and QT interval; they failed to find an association between morphine and QT interval, while methadone significantly increased QT interval.[41] Hämmig et al., demonstrated that treatment with slow-release oral morphine (SROM) was associated with significant effects on the QT-interval; however, the mean QT-interval associated with methadone was significantly longer than that under SROM.[42] Available data on morphine are scarce, and a majority of evidence confirms its safety in the context of cardiac electrical activity at least in routine doses.[15] The present study found that the QT interval is prolonged in 59.3% of opium users, and any of non-opium users and this difference was statistically meaningful. A study conducted by Wallner et al., on consecutive therapy-seeking opiate addicts demonstrated that the most common ECG change was QT prolongation (13%).[43] It seems chronic opium consumers have a higher susceptibility to coronary artery disease and an overall increase in their ECG abnormalities in comparison with non-opium users.[31]

In our study, male gender and older age were associated with a 3.68- and 1.04-fold increased risk of QTc prolongation in user group. Similarly, Ma et al., could find an association between male gender and older age with QT interval prolongation in general Chinese population. In their primary result, female sex was introduced as a risk factor. Meanwhile, after using the clinical diagnosis criteria for long QT syndrome(setting 450 ms for men and 470 ms for women), they found female seems to be less likely for long QT syndrome in the population.[28]

However, unlike Wedam's study, we could not find an association between dose of opium consumption with QT interval prolongation.[40] A study conducted by Anchersen et al., showed

that QT interval is positively prolonged with methadone dose. Our study did not detect dose-dependent relationship between opium and QT prolongation. Methadone contrary to opium might have had a cumulative dose effect on QT interval.[36]

Raw opium is a mixture of non-alkaloidal constituents and more than 40 individual alkaloids.[7] Different substances and drugs are added to opium before introducing into the illegal market. These adulterants may produce various effects that generate deep concerns in view of health hazards, clinical consequences, and research inferences.[44] Based on the current data and to our knowledge, there are no studies on the effect of opium on QT interval in humans. Najafipour and Joukar in their animal study showed that opium smoking in case of hypercholesterolemia remarkably increased the incidence of fatal arrhythmia. This effect was not triggered by changes in the QT interval.[45]

There are controversies regarding how raw opium might influence cardiovascular system, since the opium-related studies have inherent limitations and for several reasons required data on opium are not conclusive for clinical purposes and on account of the diverse opium constituents per se.[9,44,46] Although the present study has achieved important findings denoting the higher frequency of QT interval prolongation in opium users, but critical points concerning the correlation of these findings with clinical outcome including ventricular arrhythmia, TdP, and sudden death and risk rating while opium is compared to other opioids remains unclear. We compared the findings of this study with opioid drugs, such as methadone that are pure opioid agonists and are administered with specific fixed doses. Opium tincture, a medicinal product of opium, is not included in this study. The study was monocentric and encompassed a limited study population investigated in a tertiary-care hospital. The study cases have been consuming unidentified opium material in a single province that might not be necessarily identical to the samples found in other regions of country.

Conclusion

The findings of this study indicated that opium use is associated with QTc interval prolongation. The study presents no association between opium use and QTc interval prolongation with respect to dose and time spent in opium consumption. Further similar study is required to be conducted at multicentric level involving heterogeneous proportion of participants with different opium supplies.

Acknowledgments

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