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Morphine Post-Conditioning Effect on QT Dispersion in Patients Undergoing Primary Percutaneous Coronary Intervention on Anterior Descending Cardiac Artery: A Cohort Study

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Abstract

Introduction: QT dispersion is the difference between the maximum and minimum QTc interval in a 12-lead electrocardiogram (ECG). Some researchers have demonstrated the effects of an increase of QT-d in STEMI and its reduction with successful therapy. The aim of this study was to investigate the morphine post-conditioning effect on the QT dispersion in patients undergoing primary percutaneous coronary intervention (PCI) on anterior descending cardiac artery.

Methods: This cohort study was conducted on STEMI patients admitted to the Hospital of Imam Reza (AS), Mashhad, Iran, from March 2015 to February 2016 who were undergoing primary angioplasty on the anterior descending cardiac artery. The patients were divided into two groups based on the intake or non-intake of morphine (5 mg morphine for the period of 30 minutes prior to PCI). Parameters, including age, gender, history of diabetes, and blood pressure as well as admission and 24 hours after PCI ejection fraction (EF) and QT-d, were recorded in all patients and compared between the two intervention and control groups. Independent and paired t-tests and chi-square test were used to compare the qualitative and quantitative data between the two groups using SPSS version 19 software.

Results: The present research was performed on 77 patients (61 males) with mean age of 58.71±11.84 years in the two groups of morphine consumption before PCI (n=46) and control (n=31). No statistical difference was found among the groups in age, gender, diabetes, hypertension, and onset of symptoms until primary PCI. Admission electrocardiogram QT-d value in the positive exposure group showed no significant difference with the control group, but QT-d value at 24 hours after PCI was lower in the positive exposure group than in the control group (morphine versus control: 40.32±6.98 versus 59.64±8.89; p=0.000). QT-d value 24 hours after PCI compared with the admission QT-d value was significantly reduced in both groups. The mean decrease of admission QT-d relative to QT-d 24 hours after PCI was higher in the positive exposure group than in the control group, and this difference was also statistically significant (morphine versus control: 48.65±9.95 versus 25.74±6.66; p=0.000).

Conclusion: The findings of the current survey demonstrated that morphine consumption before PCI can further reduce QT-d value in an electrocardiogram for PCI as compared to patients who did not take morphine before PCI.

Keywords: Morphine, Angioplasty, Electrocardiogram, QT-Dispersion

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1. Introduction

Acute myocardial infarction is still a prevalent and debilitating disease (1). The extent of infarction is the most important determining factor in the recovery of stroke and mortality rate (1). Thus, the restrict extent of myocardial injury is the proper way to reduce heart failure and improve the prognosis of patients after stroke (2, 3). In the past 15 years, significant improvements have been achieved in the prognosis of patients with acute myocardial infarction (4, 5). Interventionist actions such as PCI and thrombolysis are effective therapeutic options to treat and cause coronary reperfusion following myocardial infarction (6). However, the mortality rate of patients with acute myocardial infarction within the first year is still high at about 10% (7, 8). The high mortality rate (despite considerable advances in treatment methods) seems to be related to a phenomenon known as myocardial reperfusion injury, which was introduced by Jenning and Sommers for the first time in the 1960s (9). During this condition, structural and functional damages will appear in the myocardial muscle if reperfusion is acute. Therefore, myocardial injury caused by reperfusion is one of the therapeutic goals of MI. Several clinical studies have been designed in this regard (10). It was recently demonstrated that there are mechanisms such as ischemic pre-conditioning and post-conditioning that protect the heart against reperfusion injury (11). Previous studies have hypothesized that the post-conditioning probably exerts a protective effect on the heart by prolonging the temporary acidosis in the period after reperfusion (11). The post-conditioning process protects the heart muscle against reperfusion injury through applying short and temporary episodes of involved vascular occlusion (12). It was recently shown that some drugs could be used in the process PostC (also known as pharmacological PostC) (13). In other words, the PostC can be carried out mechanically, where it is required to frequently blow and deflate a balloon during angioplasty; this can lead to complications such as plaque rupture, while no problems are found with drugs such as anesthetics and opioids (14). The post-conditioning effects of opioids can apply through delta receptors by adjusting the mPTP opening, and this effect disappears with the administration of antagonists such as naloxone. So far, several in vitro studies have demonstrated a cardio-protective effect with morphine pharmacological PostC (11, 15-17). The QT interval is one of the parameters indicating the ventricles' electrical activity, which depends on the depolarization and repolarization (18). The QT-dispersion is the difference between the maximum and minimum QTc interval in a 12-lead electrocardiogram (ECG), showing the heterogeneity of repolarization in different points of the ventricles (19). Various studies have shown that QTd is associated with arrhythmia in different heart diseases, including coronary artery disease, long QT syndrome (LQTS), and heart failure (20-23). Its relationship also has been proven with ischemic heart disease (IHD) and sudden cardiac death (SCD). Some researchers have shown an increase of QT-d in STEMI. The QTd variability has been reported to be associated with myocardial viability in the setting of acute STEMI, and successful thrombolytic therapy has resulted in the reduction of QT-d (20-23). The aim of this study was to investigate the morphine post-conditioning effect on the QT dispersion in patients undergoing primary PCI on anterior descending cardiac artery.

2. Material and Methods

2.1. Study populations and design

This cohort study was conducted on patients undergoing angioplasty admitted to the Emergency Department of Hospital of Imam Reza (AS) in Mashhad, Iran, from March 2015 to February 2016.

2.2. Selection criteria

2.2.1. Inclusion criteria

The patients with anterior myocardial infarction together with ST segment elevation in the electrocardiogram who underwent emergency angioplasty were included to this study.

2.2.2. Exclusion criteria

Exclusion criteria were 1) bundle branch block with QRS> 120ms or CAVB on ECG; 2) atrial fibrillation; 3) opium addiction; 4) history of previous MI or heart surgery; and 5) contraindications for morphine (respiratory depression and BP <90).

2.3. Sample size

Because no study had examined the QT-d parameters for morphine post-conditioning, and our target parameter was QT-d changes, also given the number of patients undergoing PCI on the left anterior descending (LAD) coronary artery in the center as well as the project period, the present survey was conducted on 80 patients as a pilot study.

2.4. Data Collection

Age, gender, and history of diabetes and hypertension were recorded using a pre-designed checklist for all patients. Positive history of diabetes was considered for patients who were treated with anti-diabetic medications with

previous known diagnosis or hospitalized patients who had criteria of the American Diabetes Association. In addition, positive history of hypertension was defined as patients who were treated with antihypertensive medications with known previous diagnosis of hypertension or matched with criteria according to the Joint National Committee 7 (JNC 7) during hospitalization. Then, the onset of symptoms until primary PCI, use or non-use of morphine before PCI, admission echo ventricular ejection fraction, and admission QT-d were recorded for patients. QT-dispersion calculation based on the difference between the shortest and longest QTc in one 12-lead electrocardiogram was done by one researcher. Also, only one cardiologist fixed in the emergency department recorded ventricular ejection fraction according to the reports of echocardiogram device.

2.5. Exposure and outcomes

Exposure in this study was intake of 5 mg morphine for the period of 30 minutes prior to PCI. The patients were divided into two groups of positive exposure and control based on the intake of morphine (positive exposure) or non-intake of morphine (control). The outcome of this study was to evaluate the electrocardiographic QT-d 24 hours after PCI.

2.6. Ethics

This study was conducted on the supervision of the Ethical Committee of Mashhad University of Medical Sciences (Code: 922806). Although there were no additional interventions rather than the routine medical procedures for studied patients, they were free to exit the study whenever they decided. Moreover, the researcher was completely in charge of any possible harms for the patients during and after the study period.

2.7. Statistical analysis

The data after gathering were entered into IBM SPSS Statistics for Windows, (Version 19.0, Armonk, NY: IBM Corp). The descriptive-quantitative data were presented as graphs and tables, and then central tendency and distribution were calculated for them. Chi-square test for qualitative variables and independent t-test for quantitative variables were used to analyze differences in findings between the two groups. Paired t-test compared QT-d values of initial and 24 hours after PCI in each of the groups. P-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline results

In this study, 77 patients undergoing primary PCI (61 males and 16 females) were studied. There was no statistically significant difference between the positive exposure group before PCI and the control group for gender, age, history of hypertension and diabetes and the onset of symptoms prior to PCI (Table 1). The mean percentage of admission EF was 31.6±6.85%, minimum 20%, and maximum 40% (Table 1). The two groups had no significant difference for admission electrocardiographic QT-d with a mean of 87.53±12.97 ms for all patients.

Table 1. Underlying variables between the intervention before PCI and control groups

Variables	Morphine consumption before PCI (*n*=46)	Control (*n*=31)	*p*-value
Gender, male / female (*n*)	10/36	6/25	0.801
Age, years (mean ± SD)	58.28±11.6	59.35±12.29	0.700
Hypertension, (*n*)	18	19	0.056
Diabetes, (*n*)	16	9	0.597
Onset of symptoms prior PCI, hours (mean ± SD)	4.58±1.08	4.83±1.00	0.307
Ventricular ejection fraction, % (mean ± SD)	34.34±6.54	32.58±5.14	0.421
Admission QT-d, ms (mean ± SD)	88.97±13.89	85.38±11.36	0.236

3.2. Outcomes

The mean QT-d 24 hours after PCI was lower in the positive exposure group compared with the control group (p=0.000) (Table 2). Moreover, the mean changes of admission QT-d relative to QT-d 24 hours after PCI was higher in the positive exposure group than in the control group (p=0.000) (Table 2). In addition, the results indicated that the QT-d value significantly increased 24 hours after the PCI compared with admission (p=0.000) in both groups (Table 3).

Table 2. Outcomes examined between the intervention before PCI and control groups

Variables	Morphine consumption before PCI (*n*=46)	Control (*n*=31)	*p*-value
Electrocardiographic QT-d 24 hours after PCI, ms (mean ± SD)	40.32±6.98	59.64±8.89	0.000
Difference between QT-d values of admission and 24 hours after PCI, ms (mean ± SD)	58.28±11.6	25.74±6.66	0.000

Table 3. Evaluation of QT-d in terms of baseline and 24 hours after PCI in two studied groups

Variables	Admission QT-d, Ms (mean ± SD)	QT-d 24 hours after PCI, Ms (mean ± SD)	*p*-value
Morphine consumption before PCI (*n*=46)	88.97±13.89	40.32±6.98	0.000
Control (*n*=31)	85.38±11.36	59.64±8.89	0.000

4. Discussion

The current study was conducted to evaluate the morphine post-conditioning effect on QT-d changes in patients undergoing primary PCI on anterior descending cardiac artery. The results revealed that the positive exposure group had significantly lower QT-d value 24 hours after PCI compared with the control group. Also, the rate of decline in the QT-d value 24 hours after PCI relative to admission was higher in the positive exposure group than the control group. All the evidence suggests that morphine consumption before PCI had significant relationship with further reduction in QT-d. In this study, QT dispersion is originally a crude and approximate measure of impaired repolarization and, based on previous studies, further increase of QT-d goes along with the worse prognosis. Therefore, it is predicted that, after any action performed to treat ischaemic heart disease, its value should be reduced compared with before treatment. The point observed in a recent study was reduction in QT-d value after primary PCI in all patients were exposed and not exposed to morphine. In the current study, the average admission QT-d was about 87.53 ms. This means that our patients were at high risk for overall mortality, cardiac death, and sudden death compared with the findings of Macfarlane (24) in a four-year follow-up on patients with QT-d over 60 ms who were considered as a high-risk cardiac group. According to another study (25), those with QT-d greater than 58 ms were considered as patients with a high risk of mortality. Interestingly, QT-d was reduced in patients around 40 ms 24 hours after PCI and reached to about 48.10 ms. This means that, based on QT-d, PCI as a suitable therapeutic strategy improves perfusion and resolves cardiac repolarization abnormalities. However, the first important finding in our study appeared in the same phase, i.e., 24 hours after primary PCI; thus, patients who consumed morphine for any reason prior to primary PCI had significantly lower levels of QT-d compared with patients who did not take morphine. Our subsequent analysis also indicated that the reduced rate of QT-d value in patients taking morphine was about 23 ms more than the group with no morphine. The analysis of this 23 ms difference in reducing QT-d between the two groups based on the findings of other studies demonstrates reduced mortality rates of over 10% per 10 ms decrease in QT-d, thus indicating the importance of morphine post-conditioning effect (20, 25, and 26). But quite apart from the possible influence of morphine on the QT-d, which shows positive effects on the cardiac polarization, the morphine post-conditioning effects by taking preventive mechanisms against myocardial reperfusion injury is an issue that can be useful in the future if proven. The myocardial reperfusion injury is a phenomenon that was introduced for the first time in the 1960s by Jenning and Sommers (5). During this condition, structural and functional damages will appear in the myocardial muscle if reperfusion is acute; this has been associated with an increase in the extent of myocardial necrosis in animal models and accompanied in humans with ventricular remodeling and ventricular arrhythmias and no-reflow, thus exacerbating prognosis in patients with AMI. Thereby, reducing myocardial reperfusion injury is one of the therapeutic goals of MI.

This study was an attempt to further understand the role of morphine against myocardial reperfusion injury. So far, few studies have examined the association of morphine with QT-d. Most studies evaluated the morphine post-conditioning cardiac effect in rat models via measurement of infarcts by staining methods such as triphenyltetrazolium chloride, TTC (16). Also, despite being an old hypothesis of morphine post-conditioning cardiac effect since 1996 (17), few studies have been so far done in this regard. The first study conducted to evaluate the morphine post-conditioning cardiac effect on the extent of myocardial infarction in rats showed that the hypothesis is correct. According to this group of researchers, the possible cause of morphine post-conditioning cardiac effect was due to the opioids receptor-KATP channel signaling in a rat heart (17). Ling Ling et al. (27) carried out a study to assess intrathecal morphine post-conditioning effect in rat myocardium. The authors concluded

that morphine intrathecal administration could induce a morphine post-conditioning cardiac effect because it involves the central opioids receptors but not the peripheral non-opiate receptors. The most similar animal study with our research was a survey conducted by Gao et al. on 40 rats to determine the morphine conditioning effect on ischemic injury/myocardial reperfusion (28). In this study, the rats were divided into four equal groups; their chests were opened without ligating the left coronary artery, with ischemia-reperfusion (Group I/R), ischemic preconditioning (Group IPC), and morphine post-conditioning cases (Group MOR) receiving intravenously 0.3 mg/kg morphine five minutes prior to reperfusion. The LAD coronary arteries were ligated for 30 min in rats of five groups and then were re-perfused for 90 min. Terminal deoxynucleotidyltransferase-mediated dUTP nick-end labeling (TUNEL) methods were used to detect cardiac apoptosis quantitatively in the current research. The results revealed that the serum malondialdehyde (MDA) level reduced and the enzyme activity of superoxide dismutase increased in all groups except Group I/R. Reduced ischemia-reperfusion injury leading to myocardial apoptosis, reduced myocardial infarct size, decreased MDA level and increased SOD activity were observed significantly in the morphine post-conditioning group. This means that morphine post-conditioning can have an in vivo protective impact on myocardial ischemia-reperfusion injury in rats. However, the authors suggested further investigation on the effects of morphine post-conditioning on myocardial ischemia reperfusion injury. In addition, Zhang et al. (29) during a clinical trial studied the morphine-induced post-conditioning effect on protection role against myocardial ischemia/reperfusion injury in consecutive children undergoing corrections of Tetralogy of Fallot (TOF). The positive exposure group was injected by 0.1 mg/kg morphine via cardioplegia directly with a needle into the aortic root and with delivery to the heart within 1 min starting at 3 min before removing aorta cross-clamp. Cardiac troponin I (cTnI) was tested before surgery and 4, 8, 12, 24, and 48 hours after reperfusion. The morphine-induced post-conditioning decreased maximum cTnI release after surgery (0.57±0.15 ng/mL) than in the control group (0.75±0.20 ng/mL) ($p<0.0001$). These patients during the first postoperative 24 hours had less peak inotropic score (5.7±2.4 versus 8.4±3.6, $p<0.0001$), lower duration of mechanical ventilation (20.6±6.8 versus 28.5±8.3 h, $p<0.0001$), shorter duration of hospitalization in ICU (40.4±10.3 versus 57.8±15.2 h, $p<0.0001$), more left ventricular ejection fraction (0.57±0.15 versus 0.51±0.13, $p=0.0467$) and higher cardiac output (1.39±0.25 versus 1.24±0.21 L/min, $p=0.0029$), respectively, compared with the control group. Finally, the authors concluded that morphine-induced post-conditioning might provide enhanced cardio-protection against ischemia/reperfusion injury in children undergoing corrections of TOF. As previously mentioned, none of the studies examined morphine post-conditioning effect on myocardial ischemia/reperfusion injury using QT-d in human samples. Therefore, the current study was carried out for the first time to determine the relationship between morphine post-conditioning effect and QT-d values, and, accordingly, the obtained results cannot be compared with the findings of other studies. However, based on the results achieved in this study and regarding animal researches, it can be concluded that the reports of morphine post-conditioning effect is encouraging though discussion on the exact kinds of ischemic post-conditioning algorithm is still ongoing to use in clinical settings.

5. Limitations and suggestions

The present research was faced with a variety of limitations. In this study, only the morphine post-conditioning effect was investigated using QT-d after PCI, while it was better to be assessed using serum markers such as troponin. Because this evaluation was conducted as a pilot, so many confounding factors were controlled by designing exclusion criteria. However, further studies should be designed as a clinical trial with a minimum of bias using random and blinding allocation in addition to considering more underlying variables to match patients in both groups. Moreover, it is recommended that further researches should be conducted to verify the morphine post-conditioning effect on QT-d, taking into account the different situations of patients and various vascular involvement.

6. Conclusions

The findings of this study indicated that morphine post-conditioning apparently led to more reduction in QT-d in patients undergoing primary PCI on anterior descending cardiac artery. However, the results could not be generalized considering the type of study design, limited sample size, and failure to control with other cardiac markers. In addition, further researches should be performed on the morphine post-conditioning effect.

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Conflict of Interest:
There is no conflict of interest to be declared.

Authors' contributions:
All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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