Role of serum myeloperoxidase, CPK, CK-MB, and cTnI tests in early diagnosis of myocardial ischemia during ERCP

BILIARY

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ABSTRACT

Background/Aims: Some patients may experience retrosternal pain during ERCP, which may be a pioneer of a serious myocardial problem, and early diagnosis is very important for the prognosis and management. In the study, we aimed to investigate the role of serum cardiac biomarkers, such as myeloperoxidase (MPO), creatine phospokinase (CPK), creatine kinase- myocardial band (CK-MB), and cTnI, on early diagnosis of myocardial ischemia during endoscopic retrograde cholangio pancreaticograpy (ERCP) procedures.

Materials and Methods: In this prospective observational study, ERCP patients were separated into ischemic cardiac (n:48) and non-ischemic (n:76) groups. Serious cardiac, kidney, and liver disease patients were excluded from the study. Changes in electrocardigrapy (ECG), blood pressure, pulse rate, oxygen saturation, and serum MPO, CPK, CK-MB, and cTnI levels were investigated before and after the ERCP. Results were evaluated statistically (p<0.05).

Results: Mean age was 59.76±16.62 (55♀, 69♂). Only one patient had clinically unimportant retrosternal pain (0.8%). ST-elevation was detected in 10.4% (n:5), ST-depression in 12.5% (n:6), and negative-T in 31.3% (n:15) of ischemic patients during ERCP. Systolic and diastolic blood pressure and pulse rates in both groups and oxygen saturations in the ischemic group were reduced after ERCP. Significance was not detected with MPO and CPK tests. CK-MB levels showed an increase after the ERCP in the non-ischemic group (p<0.001). cTnI means were higher among the ischemics when pre- and post-ERCP periods (p:0.001) were compared.

Conclusion: Clinically unimportant retrosternal pain, T negativity, and ST segment changes as well as reduced systolic, diastolic blood pressure, and heart rates can be seen during ERCP. MPO and CPK levels remain insignificant if myocardial injury does not develop. Increased CK-MB levels in non-ischemic patients and increased cTnI levels in ischemics may be seen.

Keywords: Endoscopic retrograde cholangiopancreatography, myeloperoxidase, myocardial ischemia, cardiac troponin-I, CPK, CK-MB

INTRODUCTION

Early diagnosis of myocardial ischemia is essential for management and prognosis of the patient. Myocardial cell injury is closely related with recruitment and activation of polymorphonuclear neutrophils (PMNs) (1,2). In acute coronary syndromes (ACS), PMNs have been shown to undergo increasing degranulation within coronary circulation. One important degranulation material is myeloperoxidase (MPO), a hemoprotein that has proatherogenic properties caused by oxidizing low density lipoprotein (LDL)-cholesterol (3), activating metallo-proteinases (4), reducing nitric oxide bioavailability, and impairing its vasodilatory and anti-inflammatory functions (5,6). MPO is suggested as an early reliable marker for ACS. Serum levels of MPO have been shown to predict risks of subsequent major adverse cardiac events, ranging from nonfatal myocardial infarction to death-thus, the need for revascularization in patients presenting with chest pain (7) or ACS (8). Increased serum levels of MPO have also been demon-

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strated to predict the presence of angiographic coronary artery disease (9). One study, comparing MPO levels of patients with stable and unstable ischemic heart disease, found that MPO levels were significantly higher among patients with ACS (10). Troponin-negative ACS patients who had higher MPO concentrations on admission became troponin-positive after 6 hours (11). In a meta-analysis study involving 3902 patients, Chen Y. found that ACS patients with initially high MPO levels had a poor long-term prognosis (12).

Retrosternal pain and myocardial ischemia have been documented in some patients during ERCP (13-15). Fisher et al. (16) reported that myocardial injury was observed in 8% of procedures after ERCP, as evidenced by an elevation in serum cardiac troponin-I, and that myocardial ischemia might be associated with post-ERCP pancreatitis. In contrast, on the basis of serum cardiac troponin-T concentrations, Martin et al. (17) found that myocardial ischemia during ERCP was transient, without progression into myocardial damage, and was not associated with clinical outcome. Silent myocardial ischemia, defined as myocardial ischemia in the absence of angina, is one of the most common presentations of coronary artery disease. Holter monitoring is useful in the detection of silent ischemia (18). Indeed, Gibson et al. (19) emphasized that detection of myocardial ischemia via ambulatory Holter monitoring is of greatest diagnostic and prognostic importance. Interestingly, no sign of existing coronary artery disease was found in patients developing ST deviation during ERCP when evaluated with a 12-lead exercise ECG test (18).

Our aim was to investigate the role of serum cardiac biomarkers, such as MPO, CPK, CK-MB, and cTnI, on early diagnosis of myocardial ischemia during ERCP procedures and evaluate the frequency of retrosternal pain, changes in ECG, systolic and diastolic blood pressure, pulse, and oxygen levels of patients.

MATERIALS AND METHODS

Study design

This observational comparison study was performed in the gastroenterology clinic of the Bezmialem Vakif University Hospital from December 2011 through May 2012 after receiving local ethical committee approval (18-01-2012/212). Patients who were sent for choledochal stone removal were grouped as ERCP patients who were diagnosed in advance of having ischemic cardiac problems (n:48; the control group) and ERCP patients with no cardiac problems (n:76; the non-ischemic group, the study group). Changes in ECG, blood pressure, heart rate, oxygen saturation levels, and serum MPO, CPK, CK-MB, and cTnI levels were investigated before and after the ERCP. Results of the study were compared statistically. ECG monitorization was measured by the D-II and V5 leads of a 5-lead ECG. Patients were sedated by midazolam (Dormicum®, Roche Co. Sweden) and propofol (Diprivan®, AstraZeneca Co, Sweden-UK). Midazolam was administered in doses of 0.03-0.07 mg/kg

to maintain the Ramsey sedation scale of grades II and III (20). Propofol was given intravenously in doses of 3 mg/kg/hour by infusion pump. If necessary, hyoscine N-methyl-bromide was intravenously administered in doses of 20 mg as an antispasmodic during the ERCP period. A diclofenac sodium suppository (Voltaren®, Novartis Co. Switzerland) (100 mg) was given rectally to each patient before the beginning of the ERCP. Oxygen (100%) was administered to the patients by nasal catheter (2 lt/min) with the oxygen saturation level maintained above 92% during sedation. Blood pressure and heart rates were measured by non-invasive tension monitorization.

Study population

Regardless of gender, the patients who were referred for ERCP for choledochal stone extraction were prospectively included in the study (n:124). Patient ages ranged from 23 to 87. The age of patients was between 23-87. Patients with serious cardiac, kidney, or liver disease were excluded from the study.

Laboratory methods

Two hours before and after the ERCP, changes of ECGs (normal, elevation, or depression of ST wave >2 mm, negative T wave), blood pressure, heart rate, and oxygen saturation levels, as well as serum MPO, CPK, CK-MB, and cTnI levels, were investigated. MPO levels were measured by MPO-EIA (R&D Co. Ltd, Germany) according to the manufacturer's instructions. Blood samples were assayed in duplicate and averaged methods. Creatine kinase and CK-MB were studied with Roche diagnostic kits in a COBAS C-8000 Roche autoanalyzer, creatine kinase was studied by an enzymatic UV method, CK-MB was studied by an immunological UV method, and cTnI tests were studied with chemiluminescence by Siemens kits in a Siemens Advia Centaur autoanalyzer.

Statistical analysis

The Statistical Package for the Socail Sciences (SPSS) Windows version 15 program was used for statistical analyses. Appropriateness of the parameters for normal distribution was evaluated by Kolmogorov-Smirnov test. Descriptive statistical methods were used for evaluation of the data (mean, standard deviation, and frequency). For the quantitative data, student's t-test was administered to compare the parameters of groups with normal distribution, and Mann-Whitney U-test was administered for abnormally distributed ones. Paired-sample t-test was used for intra-group comparisons, and Wilcoxon sign test was used for group comparison of parameters with normally distributed parameters. Qualitative data were compared by chi-square test. The significance was set at p<0.05.

RESULTS

The mean age of patients was 59.76±16.62, and it was higher in the ischemic group (62.4±14) than the non-ischemic group (53.38±15.87) (p<0.01). Mean ERCP duration was about 18±5 minutes, mean propofol dose was 210±30mg,

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Table 1. ECG changes in ERCP patients

		Ischemic cardiac disease		Total n (%)
		Absent n (%)	Present n (%)	
ST wave changes	Absent	76 (100%)	37 (77.1%)	113 (91.1%)
	ST elevation >2 mm	0 (0%)	5 (10.4%)	5 (4%)
	ST depression >2 mm	0 (0%)	6 (12.5%)	6 (4.8%)
Negative T wave	Absent	76 (100%)	33 (68.8%)	109 (87.9%)
	Present	0 (0%)	15 (%31.3%)	15 (12.1%)
Other changes in ECG	Previous myocardial infarction	0 (0%)	48 (100%)	48 (38.7%)
	Normal ECG	76 (100%)	0 (0%)	76 (61.3%)

ECG: electrocardigrapy

Table 2. Changes in blood pressure, heart rate, and oxygen levels of ERCP patients

		Ischemic cardiac disease		⁺p
		Absent Mean±SD	Present Mean±SD	
Systolic Blood Pressure	Pre-ERCP	118.35±10.91	121.31±15.84	0.221
	Post-ERCP	113.86±11.72	115.10±16.55	0.654
	⁺⁺p	0.005	0.002	
Diastolic blood pressure	Pre-ERCP	75.48±8.94	74.58±9.93	0.601
	Post-ERCP	70.93±9.03	70.58±7.68	0.825
	⁺⁺p	0.001	0.005	
Heart rate	Pre-ERCP	77.13±13.09	80.04±8.77	0.141
	Post-ERCP	74.09±13.93	76.41±10.22	0.290
	⁺⁺p	0.019	0.002	
O_2 (%)	Pre-ERCP	95.72±2.55	95.00±5.63	0.332
	Post-ERCP	95.09±3.85	93.87±5.99	0.172
	⁺⁺p	0.116	0.030	

ERCP: endoscopic retrograde cholangio pancreaticograpy
⁺Student t-test
⁺⁺Paired sample t-test

and mean midazolam dose was 2.5±1.1 mL. Hyoscine N-methyl-bromide was used at a dose of 20 mg for all study patients during ERCP.

The patient (0.8%) who complained of retrosternal pain was from the ischemic cardiac group and had a past history of coronary attack. Despite retrosternal pain and ST elevation of more than 2 mm and no change in serum cardiac biomarkers, his symptoms resolved within 15 minutes.

ECG changes were detected only in the ischemic group during the post-ERCP period. ST segment depression (≥2 mm) was present in 12.5% (n:6), ST elevation (≥2 mm) was present in 10.4% (n:5), and a normal ST wave was present in 77.1% (n:37). A negative T wave was detected in 31.3% (n:15) of the ischemic group patients (Table 1).

If compared according to pre-ERCP (118.35±10.91 mm Hg in the non-ischemic and 121.31±15.84 mm Hg in the ischemic group) and post-ERCP (113.86±11.72 mm Hg in the non-ischemic and 115.10±16.55 mm Hg in the ischemic group) periods, mean systolic blood pressure of both groups decreased after the ERCP procedure (p:0.005 and p:0.002). Systolic blood pressure in both groups was found to be statistically significant when comparing pre-ERCP and post-ERCP periods (p:0.001 and p:0.005, respectively), but blood pressure was reduced in the post-ERCP period. Mean heart rate in both groups was also statistically significant (p:0.019 and p:0.002, respectively) and low in the post-ERCP period. The mean oxygen concentration level was reduced in the post ERCP period in the ischemic group -a statistically significant difference between the pre- and post-ERCP periods (p:0.03)- but insignificant in the non-ischemic patients (p:0.116) (Table 2).

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Table 3. MPO, CPK, CK-MB, and cTnI findings of ERCP patients

| | | Ischemic cardiac disease | | |
		Absent Mean±SD (median)	Present Mean±SD (median)	p
MPO	Pre-ERCP	6.73±2.03	7.41±2.30	0.089
	Post-ERCP	6.73±2.09	7.43±2.35	0.086
	p	0.948	0.735	
CPK	Pre-ERCP	108.75±170.61 (65)	71.81±49.65 (55.5)	0.340
	Post-ERCP	92.61±125.91 (65)	78.43±73.16 (51.5)	0.469
	p	0.138	0.607	
CK-MB	Pre-ERCP	17.27±25.05 (12.80)	14.07±4.91 (13.05)	0.587
	Post-ERCP	19.74±23.29 (15.55)	15.90±7.39 (13.87)	0.112
	p	0.001	0.191	
cTnI	Pre-ERCP	0.00±0.01 (0)	0.01±0.03 (0)	0.001
	Post-ERCP	0.00±0.01 (0)	0.04±0.11 (0)	0.001
	p	0.721	0.745	

MPO: myeloperoxidase; CPK: creatine kinase; CK-M: creatine kinase-MB; cTnI: cardiac troponin-I
Student t-test was used for comparison of between groups; paired-sample t-test was used for comparison inside of groups.
Mann-Whitney U-test was used for between groups, and Wilcoxon sign test was used for comparison inside groups.

A statistically significant difference was not present in the means of the levels of MPO and CPK (p>0.05) in either group of patients during the pre- and post-ERCP periods (p>0.05).

CK-MB levels showed a statistically significant increase after the ERCP procedure in the non-ischemic group (p<0.001). Although cTnI means were insignificant in the pre- and post-ERCP periods of both groups (p>0.05), they were generally higher among the ischemics than in the non-ischemics when comparing the pre-ERCP and post-ERCP periods (p:0.001) (Table 3).

DISCUSSION

In practice, patients sometimes present with not only retrosternal pain but also changes in ECG, blood pressure, pulse, oxygen saturation level, and results of some laboratory tests during ERCP. In general, clinically mild myocardial injury resolves without being dangerous; it does not typically become severe. According to Bell, over 50% of the complications and 60% of the deaths associated with upper gastrointestinal (GI) endoscopy are cardiopulmonary-related (21). Rosenberg, the first to report about myocardial ischemia during ERCP with a 22% incidence, said that during upper gastrointestinal endoscopy, tachycardia is more important than hypoxemia in the pathogenesis of the myocardial ischemia. He explained that myocardial ischemia may be caused by a patient's discomfort or pain but also by sedative and anticholinergic drugs used during ERCP. Mechanical effects of the use of a duodenoscope may also stimulate the sensorial afferents while it moves down the esophagus and may cause myocardial ischemia (22,23). Jonston showed that myocardial ischemia developed in approximately 25% of ERCP patients, half of whom had no previous cardiac history (15). Si-

lent myocardial ischemia has been reported in the literature with different frequencies. Vieire found a 2% frequency in 50 patients (13); Lee detected a 18.3% frequency; among 71 patients, one of whom had a myocardial infarction (14), Johnston detected 22% in 41 patients (15); and Fisher reported 8%, of whom 2 died (16). Changes of ST wave in the ECG may not be related with a pre-existing cardiac problem (18). Johnston found that 22% of his patients had developed ST depression, of whom 10% showed >2 mm depression and over half had no previous cardiac history (15). In a study, cardiac ischemia occurred in 13 patients (18.3%) during ERCP, and one patient developed myocardial infarction; in this study, patients were mostly from the ischemic group than in the non-ischemic group (38.5% vs. 5.2%) (14). Among 62 patients, Martin found change in 61 of them, including one patient with a post-procedural T wave inversion but a normal troponin T level (17). A negative T wave was detected in about one-third of our ischemia group patients (n:15) as well as in 12.1% of all study patients. In Cristensen's small-scale study, 2 of 10 patients developed myocardial ischemia, demonstrated by Holter tape recording and myocardial scintigraphy (24). Only one of the ischemic group patients (0.8%) complained of retrosternal pain.

During the ERCP, reduction in blood pressure may also be caused by the medications used during ERCP, such as propofol and antispasmodics. Any other intervening causes can also disrupt the balance between myocardial blood flow and energy requirements, thereby resulting in myocardial ischemia. In Vieira's study, hypotension was presented in 1 of 50 ERCP patients (13). Cot´e et al. (25) prospectively studied 799 patients undergoing endoscopy procedures under propofol sedation, indi-

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cating that hypoxemia was present in 12.8% and hypotension was present in 0.8% of those patients. Garewal demonstrated that transient hypoxemia was present in 2% and transient hypotension (<90 mm Hg) was present in 5% of 150 American Society of Anesthesiologists (ASA) 1-3 patients (26). During ERCP, hypotension was only found in 15.4% of 71 ischemic group patients (14). Tachycardia, bradycardia, and arrhythmias may develop during the period of ischemic myocardial injury, but none of our study patients experienced them. After ERCP procedure, heart rates were typically reduced in both groups. Given the presence of coronary artery disease, the mean of the study patients' heart rates was not statistically significant before or after the ERCP (p>0.05). During the post-ERCP period, the decrease in the mean heart rate was significant in both groups (non-ischemic group 77.13±13.09 vs 74.09±13.93, p:0.019; and ischemic groups 80.04±8.77 vs 76.41±10.22, p:0.002). Presence of reduced heart rates, regardless of ischemic cardiac disease, shows that this situation is caused mostly by medications (sedatives, hypnotics, and antispasmodics) (27,28) used in ERCP. Oxygen levels of non-ischemic patients did not change before or after the ERCP procedure but decreased among the ischemics. This situation may be explained by the pump function of the myocardium. In stressful situations that require effort, such as ERCP, the pump function does not work correctly in the ischemic patients; so, oxygen levels may fall to varying degrees.

Myeloperoxidase (MPO) has been suggested as a reliable early marker for ACS associated with unfavorable clinical outcomes, demonstrated by many clinical studies (7,8,9,29). Most of the data about MPO are relevant to ACS and myocardial injury, but the literature has no data about early detection of myocardial ischemia by MPO during ERCP. Comparing the diagnostic performance of hs-cTnT and MPO in patients with coronary artery and myocardial infarction for early diagnosis of acute myocardial infarction, Khan found that the diagnostic efficacy of hs-cTnT was superior to that of MPO (29). Brennan assessed the value of plasma levels of MPO as a predictor of the risk of cardiovascular events in 604 patients with chest pain and concluded that MPO independently predicts early risk of myocardial infarction and major adverse cardiac events in the ensuing 1- and 6-month periods. MPO levels, in contrast to troponin-T, CK-MB, and c-raektif protein (CRP) levels, identified patients at risk for cardiac events in the absence of myocardial necrosis, highlighting its potential usefulness for risk stratification among patients who present with chest pain (7). Studying 1090 patients, Baldus et al. (8) concluded that MPO serum levels powerfully predict an increased risk for subsequent cardiovascular events and extend the prognostic information gained from traditional biochemical markers in patients with ACS. Chen et al. (12), in their study completed with 3902 patients, showed that ACS patients with high MPO levels had a poor long-term prognosis. Sawicki et al. (11) found that both MPO and cTnI values were significantly lower in non-ACS subjects than in patients with ACS (the 97.5th percentile was the cut-off); however, the superiority of MPO over cTnI was ob-

served in patients with unstable angina and non-ACS subjects. Considerably higher MPO concentrations were demonstrated in troponin-negative ACS patients on admission who became troponin-positive after 6 hours. In all patients with ACS, the combined evaluation of MPO and cTnI possessed remarkably higher sensitivity than assessment of cTnI alone. In our study, before and after the ERCP, a meaningful change was not seen in MPO and CPK level means in the ischemic and non-ischemic groups or between the 2 groups, because none of our study patients had a serious myocardial problem during ERCP. Only one patient complained of retrosternal pain, which resolved spontaneously within 15 minutes. The conclusion is that the outcome of statistically insignificant MPO and CPK levels can be considered normal.

Sampling time of these cardiac markers is also another issue. It is known that CPK and CK-MB and also MPO start to increase after 2-3 hours, but we need at least 6 hours to say that they are elevated or not. For the aim of diagnosis of the cardiac injury in the earlier period, we evaluated the efficacy of the tests 2 hours after the ERCP procedure. There are many articles in the literature in favor of early sampling of cardiac markers. It has been shown that MPO levels begin to increase within minutes before the other tests (30). According to Brennan et al. (7), patients with acute myocardial infarction presenting within 2 hours of onset of chest pain have been reported to have significantly higher levels of MPO than healthy controls. It has therefore been suggested that measurement of MPO may be useful for the early diagnosis of acute myocardial infarction. Collins et al. (31) have been shown that the optimal timing for measurement of cardiac troponin remains to be defined and that additional measurements of myoglobin or CK-MB are not clinically effective or cost-effective in their study, completed with 850 patients. Highly sensitive cardiac troponins were evaluated at 0, 1, 2, 3, and 6 hours samples in a study. Among patients with diagnoses other than acute myocardial infarction, baseline cTn levels were elevated above the 99th percentile, with cTnI in 13% of them (32). The high-sensitivity troponin T assay at a cut-off point of the 99th percentile was highly sensitive for the diagnosis of myocardial infarction by 2 hours after presentation and had prognostic utility beyond that of the conventional assay (33). There is recent evidence suggesting that patients with an acute myocardial infarction can be reliably identified within 3 h after admission with up to 100% sensitivity and up to 100% negative predictive value using a hs-cTn assay, indicating that observation time may be reduced to rule out acute myocardial infarction (34). Because of these reasons, it is adequate to take samples 2 hours after the procedure instead of needing to wait at least 6 hours.

Generally, the cTnI level means of the ischemic patients were higher than in the non-ischemic patients. While mean cTnI levels of the post-ERCP period were higher (0.04±0.11) than those of the pre-ERCP period (0.01±0.03), among the ischemic group (p:0.001), mean cTnI levels of the pre- and post-ERCP periods

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of the non-ischemic (0.00±0.01 vs 0.00±0.01) and ischemic groups (0.01±0.03 vs 0.04±0.11) were statistically insignificant (p>0.05). False positivity of cTnI may be seen in many situations, such as pulmonary embolism, pericarditis, myocarditis, coronary vasospasm, sepsis, congestive heart failure, supraventricular tachycardia with hemodynamic compromise, renal insufficiency, and prolonged strenuous endurance exercise. Endogenous antibodies, such as heterophile antibodies, rheumatoid factor, and other autoantibodies, are known to interfere with the immunoassay measurements of many different analytes, including the widely used Abbot AxSYM cTnI analyzer. Other sources of circulating antibodies include immunotherapies, vaccinations, or blood transfusions, which may also interfere with these immunoassays (30). Possible reasons of the increase in cTnI levels in the ischemic group may be prolonged stress and transient myocardial injury during the ERCP.

Among the non-ischemic group patients in our study, CK-MB levels showed a statistically significant increase (p>0.001) after the ERCP procedure. The increased release of non-myocardial CK-MB may be another reason for the increased CK-MB levels seen in situations, such as trauma to muscle, burns, crush injury, electrical injuries, extreme exercise, grand mal seizures, hypothyroidism, alcoholism, chronic renal failure, hyperthermia and hypothermia, intramuscular injections, and cardiac injury other than infarction (31).

In conclusion, decreases in systolic and diastolic blood pressure and heart rates of patients can be detected during and after the ERCP period. Mostly, clinically unimportant and transient ECG changes, such as negative T wave and ST segment depression, can be seen. Increased cTnI levels in the ischemic group ERCP patients were frequently present. The MPO and CPK tests are important in the early diagnosis of myocardial injury. The reason of the statistically insignificant MPO and CPK tests may be caused by lack of development of significant myocardial damage in all of our patients during ERCP.

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