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Nitrates and Calcium Channel Blockers have Protective Effects against Pain and In-Hospital Complications after ST-Segment Elevation Myocardial Infarction

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Research Article

Abstract

Background: Acute myocardial infarction (AMI) is the primary consequence of cardiovascular disease. Mortality after AMI is high due to complications from ischemic chest pain. Interventions to control ischemic chest pain after AMI should have the attention of health care providers and researchers. Therefore, the purpose of this study was to check the effect of nitrates and calcium channel blocker use on pain level and complications after AMI.

Methods and findings: A prospective design was used. The sample consisted of 380 patients with a confirmed diagnosis of ST elevation AMI. Pain level was assessed in the emergency room prior to the occurrence of any complication or receiving any medication. All other data were abstracted from medical records after the patients were discharged. 21.1% of the sample developed at least one complication during hospitalization. The mean score for severity of chest pain was 6.3 ± 2.6. The stepwise regression showed that the use of nitrates and calcium channel blockers has a protective effect against the severity of ischemic chest pain. Previous myocardial infarction and severity of chest pain increased the risk of developing complications by 191% and 111%, respectively. On the other hand, the use of beta blockers, nitrates and calcium channel blockers has a protective effect against these complications, odds ratios were: 0.91, 0.93 and 0.88, respectively.

Conclusion: Nitrates and calcium channel blocker can be used as alternatives/additional therapy for ischemic chest pain treatment in patients with ST elevation AMI.

Keywords: Ischemic chest pain; Acute myocardial infarction; Nitrates and calcium channel blockers.

1. Introduction

Since 100 years, cardiovascular disease is number one cause of death in US [1,2]. More than one third of the American populations have ≥ 1 type of CVD [3]. By 2030, 43.9% of the US population is projected to have some form of CVD [3]. The estimated prevalence rates of acute myocardial infarction (AMI), chest pain, and coronary heart disease are 7.6, 7.8 and 15.7 million, respectively [3]. It is estimated that coronary heart disease will lead to more than 1.75 million admissions per year in US [3].

Developing (low and middle income) countries account for the highest percentage of deaths (80%) due to CVD globally [4]. In Jordan, a developing low income country, cardiovascular disease is the leading cause of death resulting in 35% of the total deaths [4,5]. In the last decade, the mortality due to secondary complications of AMI increased for every 30 min that spent before treatment is started [6]. Therefore, treatment for AMI should be initiated as soon as possible to prevent complications and improve outcomes.

Acute myocardial infarction, the primary consequence of coronary heart disease, is a syndrome characterized by myocardial ischemia in association a release of biomarkers due to myocardial necrosis [7]. It has two types in which either there is an elevation in the ST segment (STEMI) or there is no elevation (NSTEMI). Chest pain in those patients usually occurs due to imbalance between oxygen supply and demand. This is either due to ischemia from vasoconstriction/ occlusion resulting from AMI (reduction of oxygen supply), or due increase work load of the heart (increase oxygen demand) [7-9]. Chest pain is very common in patients with AMI even in patients with diabetes. In a study about chest pain in patients with AMI, the pain was present in more than 93% of the sample and was sever (more than 7 out of 10) among 85% of them [10]. Moreover, all diabetic patients and approximately all non-diabetic patients complained from pain after AMI [11].

Pain stimulates sympathetic nervous system which increases the work of myocardium and its oxygen consumption [8]. This stimulation also enhances vascular reactivity, platelet aggregation, and decrease threshold of dysrhythmias [8,12]. When myocardial ischemia increases, pain becomes more sever. Therefore, any factor that either increase

oxygen demand or decrease oxygen supply will worsen the chest pain [13,14].

Different studies have shown that pain after AMI was associated with complications and poor out comes [9,13]. Patients with severe chest pain after AMI have higher levels of in-hospital complications, longer length of stay (LOS) in the intensive care units and in the hospital compared to those with mild and moderate pain [9]. Moreover, delayed pain treatment was one of the most important factors for in-hospital mortality [15]. When chest pain persisted for patients who were suspected to have AMI, it increased the risk for death producing complications by 3.8 times. Furthermore, those patients were at 2.4 times greater risk to develop AMI [16]. The duration of chest pain also plays a role in the development of AMI and its complications. Patients with longer chest pain duration were more likely to develop AMI and complications [13].

Treatment modalities for patients with AMI have been developed dramatically in the last decades. Therefore, it is highly recommended that health care team manage the cause of the ischemic pain rather than simply mask it with analgesia. The ideal treatment for ischemic pain in AMI is the early reperfusion therapy [17]. However, patients cannot be left without pain management till the perfusion is done. Current American College of Cardiology (ACC)/American Heart Association (AHA) [7] and European Society of Cardiology (ESC) [17] guidelines for treatment of pain in STEMI stated that in the absence of hypersensitivity IV morphine sulfate is the analgesic that most commonly used in this context. Other treatment modalities recommended by ACC/AHA/ESC [7,17] include: the use of oxygen, beta blockers, nitrates and calcium channel blockers (CCB). Non-steroidal anti-inflammatory agents and COX-2 inhibitors are contraindicated because they increased death rates and complications [18,19].

Recent studies [9,14] have shown that the use of morphine to treat ischemic pain after AMI did not have a protective effect against in-hospital complications. The authors concluded and recommended the use of other modalities prior to the use of morphine. These modalities included intravenous anti-platelets (i.e., aspirin) ± heparin, IV nitrates (if not contraindicated). The purpose of these medications is to decrease oxygen consumption and enhance blood supply to myocardium by vasodilation.

Current ACC/AHA/ESC [7,17] stated that nitrates can improve signs and symptoms of myocardial ischemia by reducing left ventricular preload and increasing coronary blood flow especially when vasospasm plays a significant role. They are recommended in the first 24-48 h in patients without hypotension, bradycardia and right ventricular infraction [7,17]. Moreover, Current ACC/AHA/ESC stated that CCB may be useful, to relieve ischemia, lower blood pressure or control the ventricular response rate to atrial fibrillation in patients who are intolerant of beta-blockers [7,17]. Therefore, the purpose of this study was to check the effect of Nitrates and CCB use on pain level and complications after STEMI.

2. Materials and Methods

2.1 Research hypotheses

Hypothesis 1

The use of nitrates and CCB and will be independent predictor of ischemic chest pain severity after controlling for demographic and clinical variables (age, gender, history of diabetes mellitus, history of hypertension, history of smoking, history of pervious AMI, beta blocker use and morphine use).

Hypothesis 2

The use of nitrates, CCB and ischemic chest pain severity scores will be independent predictors of complications after controlling for demographic and clinical variables (age, gender, history of diabetes mellitus, history of hypertension, history of smoking, history of pervious AMI, beta blocker use and morphine use).

2.2 Design, sample and setting

This was a prospective observational study conducted in one teaching and three private hospitals in Jordan. All patients met the following inclusion criteria: a) 18 years or older, b) a confirmed diagnosis of STEMI by a cardiologist based on the signs and symptoms, cardiac biomarkers and electrocardiogram changes, and c) welling to participate in the study. 530 patients were approached; 105 didn't agree to participate, 25 patients received either nitrates or CCB before measuring their pain level, so they were excluded from the study. Moreover, 20 patients were excluded because their data were used to check for inter-rater reliability. Based on that, the total number of patients included in the final analyses was 380.

2.3 Ethical concedaration

The principal investigator presented the study with a detailed explanation of the purpose, procedure of data collection to the IRB committee at the Applied Science Private University. The committee forwarded the recommendation of the acceptance of the study to dean, who issued the IRB approval letter. This letter was sent to the above mentioned hospitals. These hospitals acknowledged the IRB. Moreover, they accepted this IRB and agreements to conduct the study were sent to the principal investigator prior to data collection.

2.4 Data collection procedure

The principal investigator explained the study in details and the process of data collection to the research assistants. Those research assistants were critical care nursing master holders working in the emergency room; one from each hospital. The research assistants met

with each patient with a confirmed diagnosis of STEMI in the emergency room and explained the study. If the patient agreed to participate, the research assistant asked him/her to sign an informed consent including a permission to review the medical record. Moreover, they measured pain level before the patients received any medication.

Because data were collected by three research assistants, inter-rater reliability was tested. Before research assistants started data collection, they extracted data from 20 trial charts. After research assistants completed the first 10 charts, the data were compared and differences were resolved. The research assistants then reviewed the final ten charts to test inter-rater reliability. Agreement among research assistants was 97%.

2.5 Measurement of variables

After the patients have been discharged from the hospital, the research assistants collected the needed information from medical records. These data included: age, gender, marital status and smoking history. Clinically, history of diabetes mellitus, hypertension, previous AMI and previous angina were collected. Data regarding medication used including CCB, nitrates, morphine and beta-blockers were also collected from medical record. Research assistants asked the patients to rate the severity of chest pain on a scale of 0 (no pain at all) to 10 (the most severe pain in their life) in the emergency department before any use of nitrates or CCB.

2.6 In-hospital complication

Using criteria of recently published articles about in- hospital complications after AMI [8,9,20-22] the following were considered as complications in this study (i) re-ischemia evidenced by new onset of chest pain, with ECG changes or hemodynamic instability; (ii) re-infarction evidenced by elevated cardiac enzymes and standard ECG changes; (iii) sustained ventricular tachycardia (>15 s) or any ventricular tachycardia requiring pharmacological and/or electrical intervention; (iv) fine or course ventricular fibrillation; (v) unstable supra- ventricular tachycardia; (vi) acute pulmonary edema; (vii) cardiogenic shock; and (viii) in-hospital death. These complications were recorded as 1 "occurred" or 0 "did not occur".

2.7 Nitrates and CCB

Different studies [8,9,20-22] showed that the above mentioned complications usually happen in the first 0-72 h after the occurrence of AMI. For this reason, the use of nitrates and CCB in the emergency department only was included in the analyses. We did not include the use of these medications during patients stay in the ICU in the analyses to make sure that the protective effect is due to the medication use (principle of temporality; the medication was used before the complications occurred). The use of these medications was scored either 1 to indicate "used" or 0 to indicate "not used".

2.8 Data analysis

All data were analyzed using SPSS software version 21. Descriptive statics of either n (%) or M ± SD were used to describe the sample characteristics and the occurrence of complications. Hypothesis one was tested by stepwise regression. Hypothesis 2 was tested using hieratical logistic regression. All results were considered statistically significant at $p<0.05$.

3. Results

Table 1 shows the socio-demographic and clinical characteristics of the sample. More than two third of the sample was males. The majority of the sample has

Table 1. Socio-demographic and clinical characteristics (n=380).

Variables	n(%) or M ± SD
Gender	
Male	258 (67.9)
Female	122 (32.1)
Age	66.6 ± 9.8
Severity of chest pain	6.3 ± 2.6
History of hypertension	278 (73.2)
History of diabetes	140 (36.8)
History of previous AMI	250 (65.8)
History of previous angina	355 (93.4)
Has any complication during hospitalization	80 (21.1)
ICU LOS	4.45 ± 1.52
Medication use (nitrates and CCB)	
None	60 (15.8)
Nitrate alone	170 (44.7)
CCB alone	70 (18.4)
Both (nitrates and CCB)	80 (21.1)
BB use	100 (26.3)
Morphine use	71 (18.7)
Smoking	
Never smoked	122 (32.1)
Current smoker	90 (23.7)
Former smoker	168 (44.2)

AMI: Acute Myocardial Infarction; ICU: Intensive Care Unit; LOS: Length of Stay; CCB: Calcium Channel Blocker; BB: Beta Blockers

Table 2. Complications developed during hospitalization.

Complication	Number of patients (%)*
Acute recurrent ischemia	74 (19.5)
Acute pulmonary edema	15 (4.0)
Supra-ventricular tachyarrhythmia	8 (2.1)
Sustained ventricular tachycardia	7 (1.8)
Re-infarction	5 (1.3)
Cardiogenic shock	5 (1.3)
Ventricular fibrillation	4 (1.1)
In-hospital death	3 (0.8)

*More than one patient developed more than one complication

Table 3. Stepwise regression analysis for predictors of pain severity.

Predictor	Standardized β	t	Model statistics
Male gender	0.12	2.52*	R^2=0.250; F (10.367)=14.87, p<0.01
Beta blocker use	-0.13	-2.62**	
CCB use	-0.18	-2.53*	
Nitrate use	-0.1	-1.97*	

*p<0.05, **p<0.01; CCB: Calcium Channel Blockers

Table 4. Logistic regression analysis for predictors of in-hospital complications.

Predictor	Odds ratio	95% confidence interval	Wald	P value
Previous myocardial infarction	2.91	1.41-5.81	9.12	0.004
Severity of chest pain	2.11	1.11-3.89	5.71	0.03
BB use	0.91	.86-.97	6.37	0.011
CCB use	0.93	0.96-0.99	5.33	0.04
Nitrate use	0.88	.81-.96	5.91	0.02

BB: Beta Blockers; CCB: Calcium Channel Blockers

previous angina. More than one fifth of the patients (21.1%) developed at least one complication during their stay in the ICU (Table 2). More than 84% of the sample received nitrates and CCB. Hypothesis 1: The stepwise regression showed that the use of nitrates and CCB has a protective effect against the severity of chest pain (Table 3). This model explained 25% of the variance. Hypothesis two was tested by hieratical logistic regression. As shown in Table 4, severity of ischemic chest pain and history of previous AMI were associated with increased risk of complications. On the other hand, the use of beta blockers, nitrates and CCB has a protective effect against these complications.

4. Discussion

The results of this study showed that ischemic chest pain after STEMI increased the rate of in-hospital complications. The use of CCB and nitrates decreased the severity of chest pain and has a protective effect against in-hospital complications. The results of this study are in line with previous studies which showed that pain was the most important factor affecting mortality [23] and increasing risk for developing complications and AMI [9,13,16]. These results suggested that CCB and nitrates can be an alternative to other therapies (i.e., beta blocker) when they are contra-indicated for any reason.

Increasing availability of different treatments for AMI in the last decades means that there should be a continuous reappraisal of these management strategies. Despite that, medical therapy for patients with AMI remains to have an essential and vital role especially when revascularization is inappropriate and/or incomplete. Medical therapy for ischemic chest pain to control complications in patients with STEMI usually includes: Nitrates, oxygen therapy, morphine and beta blocker. CCB are used as alternatives when beta blockers are contraindicated or to achieve most favorable symptoms control [7,24]. Moreover, anti-platelet therapy should be initiated.

Oxygen therapy improves the supply to the ischemic myocardium. However, it did not reduce mortality and morbidity associated with AMI [7,25]. According to ACC/AHA/ESC oxygen should be supplemented to hypoxemic patients with (O_2 saturation <90%) or patients with respiratory distress and with caution to patients with chronic obstructive pulmonary disease. There are various evidences telling that hyperoxia may be unsafe in patients with uncomplicated STEMI, most probably due to increased myocardial injury [26-28]. Thus, routine oxygen is not recommended when SaO_2 is ≥ 90%.

Current ACC/AHA/ ESC stated that morphine is the most commonly used analgesic to relief pain in patients with STEMI when there is no history of hypersensitivity, especially for those with acute pulmonary edema. Morphine is useful in these situations due to its analgesic and anti-anxiety proprieties [25]. Moreover, morphine can cause vasodilation, decrease heart rate and blood pressure. However, there are no randomized control trails establishing the unique effect of morphine on ischemic chest pain and patient prognosis.

Recent studies [9,14] start to question the use of morphine as the first choice treatment of ischemic chest pain associated with AMI. The authors recommended that health care team member treat the underlying cause of the pain (namely ischemia) rather than masking it by analgesia. Other studies [29,30] showed that the use of morphine increased in-hospital mortality, infarct size and LOS in the hospital. Other studies showed that the use of morphine was associated a slower uptake, delayed onset of action and diminished effects of oral antiplatelet agents [28,31,32]. Moreover, AMI patients who did not use morphine have better myocardial reperfusion based on ECG findings [33].

Beta blocker has anti-ischemic proprieties when they decrease myocardial oxygen consumption by reducing heart rate and contractility [24,34]. When heart rate is decreased, diastole time and coronary perfusion increases, which improves the myocardial oxygen supply [34]. Moreover, beta blocker decreases blood pressure, and risk for

ventricular dysrhythmias [8]. Current ACC/AHA/ESC, recommended administering intravenous beta blockers at the time of presentation to patients with STEMI who are hypertensive or have ongoing ischemia and no contraindications to their use.

Different studies [35-39] showed that the use of beta blockers was associated with reduction of short and long term complications and mortality. On other hand, some studies [40-42] failed to display any significant advantage in the rate complications or mortality. In another study [8] beta blockers did not eliminate the effect of ischemic chest pain due to anxiety on complications after AMI.

There are contraindications for the use of beta blockers in the situation of AMI. These include bradycardia, hypotension, acute congestive heart failure and heart block. Patients with asthma and a history of bronchospasm should receive only selective beat blocker (i.e., Metoprolol). The dose should be titrated gradually to avoid these side effects of the medication and to achieve a target heart rate of 50-60 beats/min. Therefore, health care providers caring for patients with AMI should use additional/alternative strategies to control ischemic chest pain. These alternatives might include nitrates and CCB.

Nitrates act by improving the oxygen supply/demand mismatch. They cause both arteries and veins dilatation at the level of therapeutic doses. When the veins are dilated the preload decreases along with ventricular wall stress and myocardial oxygen demand with an end result of improving sub-endocardial perfusion. On the other hand, arterial dilatation decreases the after load and reduces myocardial oxygen demand. Most importantly, nitrates directly dilate epicardial coronary arteries, enhancing oxygen supply to ischemic areas [7]. However, these effects might be counteracted by the increase in heart rate and contractility, especially when beta blockers are not in use [24,25].

Despite the wide range use of nitrates in the treatment of ischemic chest pain for patients with AMI, there is a little objective evidence supporting this use [24]. Usually, this use is based on clinical experience and pathophysiological principles [24]. Several studies have shown that nitrates were useful in reducing ischemic chest pain [43-45]. The use of nitrates in the pre-thrombolytic era was associated with 35% reduction in mortality for patients with AMI [46]. Current AHA/ACC/ESC stated that in the absence of hypotension, right ventricular infarction, intravenous nitrates may be useful during the acute phase of AMI in patients with hypertension or heart failure. On the other hand, two large trials [47,48] did not show that nitrates have any statistically significant reduction in mortality.

CCB is another type of medication that can be used to control ischemic chest pain in patients with AMI. CCBs are a class of drugs that selectively inhibiting calcium influx through L-type calcium channels [24]. CCB reduces afterload, myocardial contractility and heart rate; therefore, they reduce myocardial oxygen consumption. Moreover they improve myocardial oxygen supply by promoting coronary vasodilatation [24]. There are three different classes of CCB according to the selectivity of cardiac versus calcium channels. First: Dihydropyridines (i.e., nifidepine and amlodipine) which have high vascular selectively. Second: Benzothiazepine (i.e., Diltiazem) which has intermediate cardiac and vascular selectivity. Third: Phenylakylamines (i.e., verpamil) the most cardio-selective and least vascular dilator.

According to ACC/AHA/ESC many randomized control trials showed that the use of CCB did not have beneficial effect on the infract size or re-infarction for patients with STEMI. However, they recommended the use of CCB to relieve ischemia and control the ventricular response in patients who are intolerant of beta blockers or with severe left ventricular dysfunction. The use of nifideipne is contraindicated because of the reflex hypotension and tachycardia [7].

Randomized controlled trials have shown that verpamil and diltiazem have reduced mortality and morbidity and ischemic chest pain for patients with NSTEMI [49-52]. Diltiazem reduced the rate or re-infarction by 52% in 409 patients with NSTEMI [53]. In another randomized control trial, diltiazem was responsible for 51% and 49% reduction in re-infarction and refractory angina respectively for patients with AMI [50].

5. Conclusion

This study showed that ischemic chest pain in patients with STEMI was associated with higher levels of complications. The use of nitrates and CCB has a protective effect. Health care team members caring for patients with STEMI should think in treating the underlying cause of the chest pain rather than treating it symptomatically with analgesics alone. Larger randomized control trails to check the effect of these medications on the outcomes of pain and complication is still warranted.

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