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Original Article

Association of pretreatment amlodipine and outcome in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention

Haleh Bodagh [1], ***Ahmad Separham*** [1], ***Shokoufeh khanzadeh*** [1], ***Leila Vahedi*** [2], ***Elaheh Mohtadifar*** [3], ***Mohammad bagher Bodagh*** [3], ***Razieh Parizad*** [1,*]

[1] Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3] Student Research Committee, Islamic Azad University of Tabriz, Iran

*** Corresponding Author:**
Address: Tabriz-University Street-Tabriz University of Medical Sciences-Shahid Madani Hospital, Tabriz, Iran. **Postal code:** 5166615573; **Tel:** +98 9143134453; **Email:** r_parizad2003@yahoo.com

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Abstract

Objectives: The current study is a retrospective cross-sectional study that reviewed 497 patients with an ST-elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention (PCI). Demographic data including age, gender, history of Hypertension (HTN), diabetes mellitus, and smoking and data related to the use of Amlodipine, pic of cardiac troponin I (cardiac enzyme), ejection fraction (EF), arrhythmia at the admission, and death after PCI extracted from the previous file. The patients were divided into two groups, the first group with a history of taking amlodipine and the second group without a history of taking amlodipine. SPSS version 26 was used for data analysis. T-tests, chi-square, and Fisher's exact were used to test the relationship between variables.

Methods: In this retrospective cross-sectional study, the medical records of 497 patients with STEMI who underwent PCI were reviewed. The data were age, gender, previous use of Amlodipine, pic of cardiac troponin I (CINI), (EF), arrhythmia at the admission, history of HTN, Diabetes mellitus and smoking, and death after PCI. Then patients were divided into two groups with (group 1) or without (group 2) a history of Amlodipine use. Student t-test, chi-square test, and the Fisher exact test were applied to investigate the associations between variables using the SPSS version 26.

Results: Out of 497 patients included, 81.3% were males with a mean age of 58.7±12.02 years, and 22.7% had a history of taking amlodipine. Patients in group 2 showed more death and MI than group 1 (OR = 1.32 [95% CI, 1.25-1.39], P=0.002) and (OR=3.93 [95% CI, 2.24-6.87], P<0.001). There were no differences between the two groups in terms of age, sex, cTnI, EF, rate of arrhythmia, the pattern of vascular involvement, kind of vascular involvement, and occlusion location (P= 0.6, 0.9, 0.09, 0.1, 0.3, 0.28, 0.29 and 0.8, respectively).

Conclusions: Amlodipine administered before MI significantly reduced the mortality rate after PCI compared to patients not taking amlodipine. The result can be attributed to the antioxidant effect, limiting the consequences of injury around reperfusion.

Keywords: Association; Amlodipine; Acute myocardial infarction; Outcome

Introduction

Cardiovascular diseases (CVD) continue to be the main cause of disease burden in the world. Outside of developed countries, the CVD burden keeps increasing, and frighteningly, there is an increase in the age-standardized rate of CVD in some countries. If the world is to reduce early mortality from noncommunicable illnesses by 30% and achieve the Sustainable Development Goals 3, it must focus on adopting existing cost-effective medications, interventions and policies (1). Among CVD, hypertension is the most prevalent disorder, worldwide. The prevalence of HTN is above 20 % in the general population, and in recent years, an increase in the prevalence of HTN has been observed (2). HTN is the main preventable risk factor for myocardial infarction (MI), CVD, and death around the world (3-5). In addition to HTN, there are other CVD risk factors such as high total cholesterol, elevated high-density lipoprotein cholesterol, smoking, glucose intolerance, and left ventricular hypertrophy(2).

Amlodipine, an L-type of voltage-gated calcium channel blocker (CCBs), is utilized in the treatment of hypertension (HTN) as a first or second-line medication, and it affects the blood pressure (BP) through vasodilation, suppression of myocardium contraction, blockade of mineralocorticoid receptor and inhibition of aldosterone effect (6). It could reduce CVD, Risk of MI, and total mortality better than other antihypertensive medications (7,8). In addition, Amlodipine can prevent stroke better than other antihypertensive agents (7,9). Although it seemed that amlodipine increases congestive heart failure (CHF) prevalence in comparison with an angiotensin receptor blocker.

(ARBs) and angiotensin-converting enzyme (ACE) inhibitors. Patients with high-risk cardiac disease can use Amlodipine safely, and this drug can have protective effects on the cardiovascular system (7,9).

However, what we know about the impact of amlodipine on MI and CVD is largely associated with studies performed before the universal use of percutaneous coronary interventions (PCIs) for the treatment of MI. The PCI is considered the first-line treatment for managing patients with ST-segment elevation myocardial infarction (STEMI) (10) and approximately 600000 patients undergo PCIs in the United States annually (11), which costs more than $12 billion (11).

Few studies investigated the effect of previous use of Amlodipine on MI complications and mortality in patients undergoing PCI. The present study was designed to determine the effect of previous use of amlodipine on the clinical outcome and mortality of patients with STEMI who underwent PCI.

Materials and Methods

Study population

In this retrospective cross-sectional study, we reviewed the medical records of all patients with STEMI who underwent PCI and were admitted to Shahid Madani's Hospital (Tabriz, Iran), training, caring, research, and referral center in North West Iran, between March 2014 and March 2020.

Patients were considered to have STEMI if they met both criteria: (I) pathologic conversion in electrocardiogram (ECG) (new pathologic Q waves) or rise in the blood level of cardiac enzymes including cardiac troponin I (cTnI) to more than twofold the normal upper limit and (II) ST-segment elevation of $\geq$ 2 mm on at least two contiguous leads of ECG.

The inclusion criteria were (I) patients with STEMI who underwent primary PCI and (II) previous use of Amlodipine. The exclusion criteria were (I) previous use of other types of antihypertensive medications (II) patients who needed to repeat PCI after primary PCI or underwent coronary artery bypass graft surgery [CABG], (III) left bundle branch block (IV) cardiomyopathies (V) severe hepatic or renal (creatinine >3.0 mg/dl) insufficiency or suspected cancer and (VI) severe valvular heart disease Figure 1.

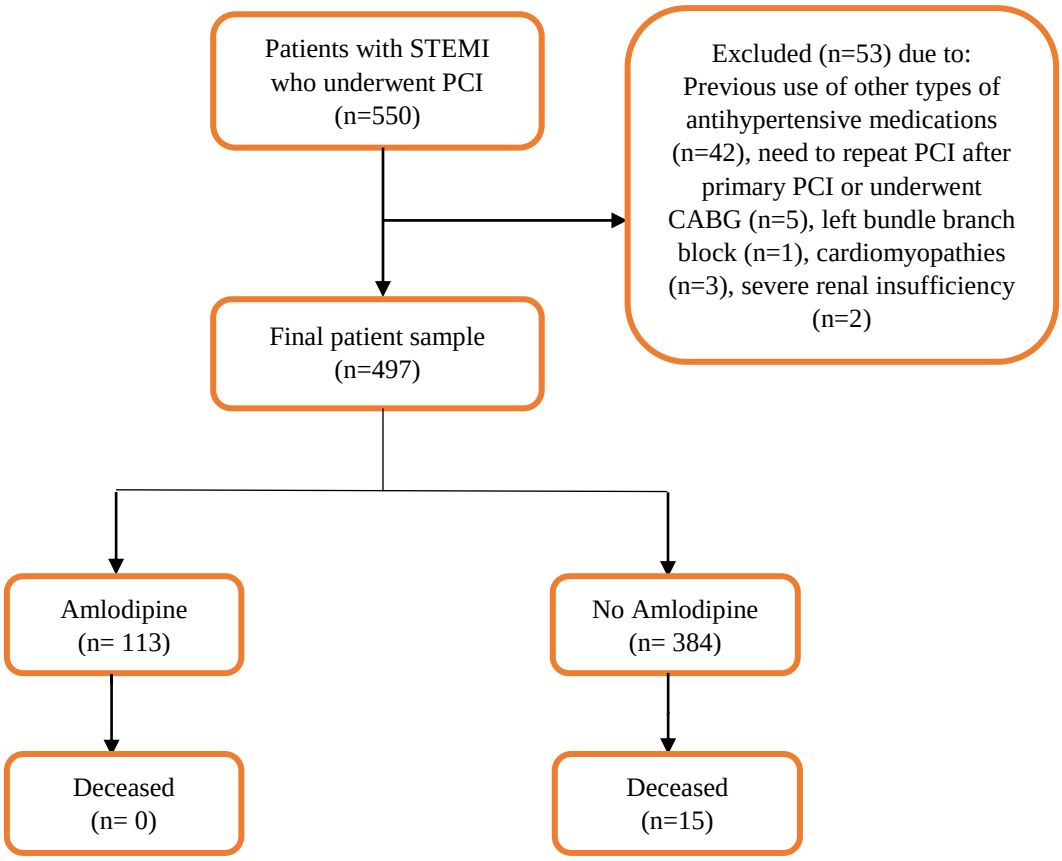

Figure1. Study flow chart diagram, STEMI indicates ST elevation myocardial infarction and PCI indicates percutaneous coronary intervention

Data collection

The data included age, gender, previous use of Amlodipine, PIC of cardiac troponin I (cardiac enzyme), EF, arrhythmia at the admission, history of HTN (diastolic BP ≥90 mmHg, and/or systolic BP ≥140 mmHg or using antihypertensive drugs) or Diabetes mellitus (history of using antidiabetic drugs, two h plasma glucose during a 75-g oral glucose tolerance test of ≥200 mg/dl, casual plasma glucose ≥200 mg/dl or fasting plasma glucose(FPG ≥126 mg/dl) or smoking (using at least one cigarette per day for one or more years), and death after PCI. Finally, patients were classified into two groups with or without a history of Amlodipine. The data collected from medical records of Madani hospital. If the file is incomplete, the information was completed by phone or visiting at the heart clinic.

Statistical Analysis

All the patients who met the inclusion and exclusion criteria were taken into account.The were analyzed using the SPSS version 26 and were expressed as the mean ±SD (standard deviation) or number (percentage). The student t-test, chi-square test, and Fisher exact test were applied to investigate the associations between variables. A P-value< 0.05 was considered statistically significant.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the deputy of research of Tabriz University of Medical Sciences (TBZMED.REC.697). Data gathering were performed after approval by the deputy of research of Tabriz University of Medical Sciences.

Results

Participant's profile

A total of 550 patients with a STEMI who underwent PCI were identified. Of them, 497 patients met our inclusion criteria and were included in our study. The mean age of patients was 58.70 ±12.02 years. The number of men was more than women (404 cases, 81.3%). Hypertension and smoking were seen in nearly

50% of patients. The mortality rate was 3% among patients.Other characteristics are shown in Table 1.

Table1. Characteristics of all patients with STEMI who underwent PCI

Variables		Frequency	Percent
Age (years)		Mean ± SD	58.70 ± 12.02
Amlodipine Use	Yes	113	22.7
	No	384	77.3
Sex	Male	404	81.3
	Female	93	18.7
HTN	Yes	205	41.2
	No	292	58.8
Diabetes Type 2	Yes	96	19.4
	No	400	80.6
Smoking	Yes	238	47.9
	No	259	52.1
Previous MI	Yes	60	12.1
	No	437	87.9
Outcome	Dead	15	3
	Alive	482	97

STEMI: ST-elevated myocardial infarction, PCI: percutaneous coronary intervention, SD: standard deviation

Then patients were divided into groups based on the usage of amlodipine (group 1) and non-usage of amlodipine (group 2).

There was no difference between the two groups regarding age and gender (*p*= .6, and .9, respectively). The previous MI rate was more common in patients with non-Amlodipine as significant (OR=3.93 [95% CI, 2.24-6.87], P<0.001). The rate of arrhythmia, the pattern of vascular involvement, the kind of vascular involvement, and occlusion location did not differ between the two groups (P=0.3, 0.28, 0.29, and 0.8, respectively) Table 2.

Table2. Associations between variables and two groups based on the usage of Amlodipine among patients with STEMI who underwent PCI

Variables		Amlodipine n=113	No Amlodipine n=384	*P*- value	OR 95% CI
Age(years)		62.74±11.42	57.52±11.95	0.6	-
Sex	Male	92(81.4)	312(77.2)	0.96	-
	Female	21 (18.6)	72(18.8)		
Outcome	Dead	0(0)	15 (100)	0.002	1.32(1.25-1.39)
	Alive	113(23.4)	369(76.6)		
Troponin enzyme	Mean±SD	6.77±7.56	8.79±9.44	0.094	-
Ejection Fraction	Mean±SD	40.48±8.68	39.25±7.85	0.1	-
Pervious MI	Yes	29(25.7)	31(8.1)	<0.001	3.93(2.24-6.87)
	No	84(74.3)	353 (91.9)		
Arrhythmia	Bradycardia	2(1.8%)	2(0.5%)	0.36	-
	V tach	2(1.8%)	4(1.0%)		
	VF	0(0.0%)	3(0.8%)		
	Negative	109(96.5)	375(97.8)		
Pattern of vascular involvement	SVD	44(38.9)	182(47.4)	0.28	-
	2 VD	43(38.1)	125(32.6)		
	3 VD	26(23)	77(20.1)		
Kind of vascular involvement	LAD	73(64.6)	227(59.1)	0.29	-
	LCX	16(14.2)	47(12.2)		
	RCA	35(31)	121(31.5)		
	Poba	3(2.70	2(0.50		
	PDA	2(1.8)	5(1.3)		

Table2. Associations between variables and two groups based on the usage of Amlodipine among patients with STEMI who underwent PCI

Variables		Amlodipine n=113	No Amlodipine n=384	*P*- value	OR 95% CI
Occlusion location	Main OM	2(1.8)	13(3.4)	0.80	-
	OM1	1(0.9)	10(2.6)		
	Ramus	1(0.9)	5(1.3)		
	Anterior	32(44.4)	191(61.8)		
	Inferior	36(50.0)	110(35.6)		
	Lateral	4(5.6)	15(4.9)		
	Septal	1(1.4)	5(1.6)		
	Posterior	7(9.7)	23(7.4)		

AV dissociation= AtrioVentricular dissociation; PVC= Premature Ventricular Contraction; V tach=Ventricular tachycardia; VF= ventricular fibrillation; cTnI=cardiac Troponin I; EF= Data are presented as mean value ± SD or number (%) of patients.

Association of Amlodipine and mortality rate

None of the deceased cases belonged to the usage of amlodipine (group 1), and it was statistically significant (*p*-value=.002) Table 2.

Association of Amlodipine and Mean troponin enzyme

There was no significant difference between the mean of troponin enzyme between the two groups (*p*=.094) Table 2.

Association of Amlodipine and cardiac ejection fraction

Examination of the relationship between amlodipine consumption and mean cardiac ejection fraction revealed a non-significant relationship (*p*=.1) Table 2.

Discussion

Calcium channel blockers (CCBs) were first developed over 40 years ago for the treatment of coronary heart disease (CHD), and their utility in HTN was quickly recognized. In addition to HTN, some arrhythmic conditions peripheral to vascular disease, and angina were among its original indications (12). Numerous meta-analyses have revealed that the risk of mortality and the incidence of angina pectoris, heart failure (HF), and stroke were lower in patients on CCB (either non-dihydropyridines or dihydropyridines) compared with active therapy or placebos(13). CCBs significantly decrease afterload, contractility, heart rate, and myocardial oxygen demand (9, 14). Furthermore, an overload of intracellular calcium kills the ischemic cells in the heart, so CCB reduces ischemia-induced cell injury in myocardia (15). However, most of the studies mentioned were conducted when the treatment of choice in MI was medical treatment. It is questionable whether these effects also exist in the age of reperfusion procedures such as PCI. Reperfusion of the ischemic cells has serious complications, including reperfusion functional stunning of the myocardium, no-reflow phenomenon, vascular damage, and arrhythmias. The two most discussed hypotheses describing these complications are free-radical-induced damage and overload of calcium, reducing mitochondrial capacity to produce ATP (16). These data suggest that antioxidants and CCB may limit reperfusion injury and ischemia, so they can improve the outcome of MI followed by PCIs. Amlodipine is a lipophilic, third-generation, long-acting dihydropyridine (DHP) CCB with several unique characteristics that distinguish it from other drugs in this class. It works by preventing calcium from entering myocardial cells and vascular smooth muscle cells, resulting in lower peripheral vascular resistance. Amlodipine is used to treat angina pectoris and HTN (9). In addition, it is effective in angina pectoris in some randomized studies (9). To develop our understanding of the effect of Amlodipine, this study assessed the role of the precious use of Amlodipine in STEMI outcomes. The results revealed that this medication was beneficial, safe, and well-tolerated in the patient with STEMI who underwent PCI. The results revealed that Amlodipine could improve the outcome of MI followed by PCIs by reducing the number of death. This finding is different from the results reported by Bjorn Jorgensen et al. who showed that administration of Amlodipine two weeks

before PTCA did not decrease death in patients with MI (17 in another study by Joseph A. Dens, a placebo or Nisoldipine 40 mg coat-core was randomly started the morning after the PCI and continued for three consecutive years. There was no difference in the death rate between the two groups (18). We can attribute it to the fact that our patients were given CCBs for a significantly extended time before MI than those of the mentioned study. Further clinical and experimental studies are necessary to determine the protective role of CCB in MI followed by PCIs. Similar to previous studies (19), it was found that prior use of Amlodipine as a CCB did not affect arrhythmias in patients with STEMI. This finding is inconsistent with the results of Kloner et al. who showed CCBs could reduce the incidence of arrhythmias in patients with MI (20) which can be explained based on the methodology. On the other hand, Richard W Parsons et al. found that serious complications and arrhythmias after MI, including atrial fibrillation, complete heart block, and ventricular fibrillation, were more likely to arise in patients on CCBs compared to the control group (21),which can be explained based on the population characteristic. So patients on CCBs had a worse clinical profile than other patients (22).

Our results showed that prior use of Amlodipine had a neutral effect on early infarct expansion because there was no statistically significant difference in EF and cardiac enzyme at the admission after MI between patients on Amlodipine and patients who did not use Amlodipine. Similarly, Hagar et al. showed that in rat models, Amlodipine does not reduce dilatation of the left ventricle, early infarct expansion, and infarct extent, even when administrated before myocardial infarction (23). Similarly, Jorgensen et al. (17, 24) and Gulmez et al.(25) found no statistically significant relationship between previous amlodipine therapy and EF after MI. However, some other studies discussed it differently. Steffen et al. showed that CCBs reduced cardiac remodeling and improved the heart's function in MI-Induced HF in Rats (26). Another study by Richard W Parsons reported a lower creatine kinase ratio in the patients on CCB or beta-blocker at admission compared with patients who did not take CCB or beta-blocker (22).We can attribute this to the difference between cardiac enzymes and CCB. Although in our study, there were some differences in the occlusion pattern between the two groups, similar to previous studies (17, 24), the number of occluded vessels was not affected by the prior use of amlodipine.On examination of the main coronary artery, including the Left Anterior Descending Artery) LAD (Left Circumflex) LCX (and Right coronary artery) RCA (Similar to Gulmez et al). (25) and Bjorn Jorgensen et al.(17, 24), we did not find any relationship between prior use of amlodipine and occlusion of these vessels.Although, our examination of the terminal branch of coronary vessels revealed partially different results. In our study, the patients with occlusion of diagonal and RIA branches were more likely to be on amlodipine; however, there was no significant relation between occlusion of OM and prior use of amlodipine. In the same line, Bjorn Jorgensen et al. did not find any relation between diagonal branch occlusion and amlodipine, and there was no difference in occlusion of OM between the Amlodipine group and placebo group. However, they did not investigate the RIA branch in their study (17, 24). Gulmez et al. did not study any terminal branches (25). As to occlusion location, they found that amlodipine had a significant effect on occlusion location. Patients with inferior MI were more likely to take amilodipine, on the contrary, patients with anterior MI were more likely not to take amlodipine. The findings are in contrast with the previous study (27, 28) that showed the site of occlusion was not affected by CCBs. Further controlled and prospective studies in this field are expected to broaden our understanding of amlodipine's role in the angiographic feature of MI.

Limitations of the study

There are several limitations in our study that need to be considered. The first limitation is the retrospective study method. The second limitation, given the short follow-up time in our study, is that the number of deaths could have been higher if a longer follow-up time had been considered. The strength of our study was the relatively large sample size.

Conclusion

The present study was designed to determine the effect of amlodipine on the outcome of patients with STEMI undergoing PCI. Results showed that administration of amlodipine appeared to prevent

cardiovascular morbidity in patients with AMI who underwent PCI. The results should be confirmed in a larger population with longer follow-up. Larger randomized controlled trials could provide more conclusive evidence for amlodipine's role in mortality in STEMI patients. In addition, more work is needed to determine whether amlodipine affects the angiographic features of STEMI.

List of abbreviations

MI: Myocardial infarction,
PCI: Percutaneous coronary intervention,
STEMI: ST-elevated myocardial infarction,
EF: Ejection fraction,
HTN: Hypertension,
cTnI: Cardiac troponin I,
CCB: Calcium channel blockers,
BP: Blood pressure,
CVD: Cardiovascular disease,
CHF: Congestive heart failure,
CABG: Coronary artery bypass graft surgery,
FPG: Fasting plasma glucose,
SD: Standard deviation

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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