Page 227 to 233

Volume 2 • Issue 1 • 2018

Research Article

Therapeutic Advances in Cardiology

ISSN: 2575-5161

Different Dose Combinations of Anisodamine and Pitavastatin in Patients with Acute Inferior Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: A Randomised Factorial Trial

Xinshun Gu*, Wei Li, Weize Fan, Xianghua Fu, Guozhen Hao and Yunfa Jiang

Department of Cardiology, the Second Hospital of Hebei Medical University, Shijiazhuang, P.R. China

***Corresponding Author:** Xinshun Gu, Department of Cardiology, The Second Hospital of Hebei Medical University, Shijiazhuang, P.R. China.

Received: July 26, 2018; **Published:** August 13, 2018

Abstract

Objective: To assess the effect of different dose combinations of anisodamine and pitavastatin regimens on prevention of no reflow (NR) and amelioration of myocardial reperfusion in patients with acute inferior myocardial infarction (AIMI) undergoing primary percutaneous coronary intervention (PCI).

Methods: Fifty-A total of 112 consecutive patients were included in this study and randomly divided into four groups: Group A (pitavastatin 2mg and anisodamine 1000ug); Group B (pitavastatin 2mg and anisodamine 2000ug); Group C (pitavastatin 4mg and anisodamine 1000ug); Group D (pitavastatin 4mg and anisodamine 2000ug). Patients underwent CAG and PCI by transradial artery access. All the angiographic results (initial TIMI, final TIMI / CTFC / TMPG) were evaluated. Systolic, diastolic and mean coronary sinus pressures were determined by invasive catheterization. A 18-lead ECG was recorded both on admission and at 90 min after PCI. The primary end point was the incidence of TMPG 3 after the procedure. Composite endpoints (cardiac death + new MI + TVR) were evaluated during the hospital stay and 30 d after discharge.

Results: After the procedure, the proportion of TMPG 3 was significantly higher in group D than that in other groups (p=0.011); the proportions of postprocedural TIMI 3 and complete STR were the highest in group D. The peak CK-MB and cTnI were the lowest and LVEF three days after the procedure was highest in group D. Anisodamine combined with pitavastatin had the synergistic effect in reducing the peak level of CK-MB with statistical significance (p = 0.001) while the synergistic effect trend in increasing LVEF without statistical significance (p = 0.284). Thrombus score 3-4 and low diastolic blood pressure (DBP) were the independent risk factors for poor myocardial reperfusion (expressed as TMPG < 3), while anisodamine 2000ug before PCI was protective for optimal myocardial reperfusion after the procedure.

Conclusions: High-dose anisodamine and pitavastatin combination can better ameliorate myocardial reperfusion and protect cardiac function in patients with AIMI undergoing primary PCI.

Keywords: *Anisodamine; Pitavastatin; No reflow; Acute inferior myocardial infarction; Primary percutaneous coronary intervention*

Volume 2 Issue 1 August 2018

Citation: Xinshun Gu., *et al.* "Different Dose Combinations of Anisodamine and Pitavastatin in Patients with Acute Inferior Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: A Randomised Factorial Trial". *Therapeutic Advances in Cardiology* 2.1 (2018): 227-233.

Introduction

No-reflow (NR) phenomenon, the important manifestation of myocardial microcirculation disorder, is the failure of blood to reperfuse an ischemic area after the physical obstruction has been removed by primary percutaneous coronary intervention (PCI) or thrombolysis [1]. The incidence and extent of NR strongly predict adverse clinical outcomes including persistent contractile dysfunction of left ventricle, malignant arrhythmias and cardiac death [2].

Acute inferior myocardial infarction (AIMI), right coronary artery (RCA) often as the infarct-related artery (IRA), is usually indicative of two features: 1) The thrombus burden is heavier, therefore, the incidence of NR is significantly increased after primary PCI; 2) The hemodynamic states are unstable, such as hypotension, bradycardia and high vagus tone, as a result, the circulatory collapse, reperfusion injury and serious arrhythmias like severe atrioventricular block possibly happen during primary PCI.

Anisodamine, an M-receptor blocker, can dilate the small vessels and improve the microcirculation [3]. Our previous studies [4-7] showed that intracoronary administration of anisodamine could effectively reverse the NR after primary PCI, which in detail displayed: 1) the improvement of the coronary antegrade blood flow simultaneously associated with the recovery of the myocardial reperfusion; 2) the increase in heart rate, blood pressure, coronary perfusion pressure and heart inotropic effect; 3) the stability of the hemodynamic states and the amelioration of the in-hospital and long-term prognosis. Accordingly, it is speculated that: anisodamine, a drug with multi-pharmacological effects, is especially suitable for AIMI.

Statins have long-term benefits when used for secondary prevention in patients with coronary artery disease. The benefits of statins in acute coronary syndromes (ACS) are seen early, before substantial lipid lowering has occurred. This suggests that pleiotropic effects of statins, not lipid-lowering effects, are responsible for these early benefits. These pleiotropic effects may include improvement in endothelial function, anti-inflammatory effects, decrease in oxidative stress, vasodilation of coronary microvessels, and inhibition of thrombogenic response [8].

The objective of this study is to assess the effect of different dose combinations of anisodamine and pitavastatin regimens on prevention of NR and amelioration of myocardial reperfusion in patients with AIMI undergoing primary PCI.

Methods

Inclusion criteria of study population

From September 2013 to June 2016, consecutive patients with AIMI presented within 12 h of symptom onset undergoing primary PCI were enrolled into this single-center randomized controlled study. Patients were eligible if they fulfilled the following criteria: (1) ischemic chest pain lasting for at least 20 min, which could not be relieved by oral nitrates; (2) clear AIMI-ECG changes during angina: new ST-segment elevation with the cut-off points ≥ 1 mm in ≥ 2-standard leads or ≥ 2 mm in ≥ 2-contiguous precordial leads or left/right bundle branch block, with or without the elevation of cardiac enzymes.

Exclusion criteria of study population

Patients were excluded if one of the following characteristics was present: cardiogenic shock, tachycardia, known allergy to every essential drug, current or previous (within 3 months) statin treatment, bleeding history, hepatic dysfunction, renal dysfunction with hemodialysis, thrombolysis, need for coronary artery bypass grafting (CABG), and contradiction to antiplatelet and anticoagulation. The study was approved by the Ethics Committee of our Institute, and written informed consent was obtained from all patients.

Eligible patients were randomly assigned in a 1:1 ratio to receive different regimens.

Dose and timing of pitavastatin administration

4mg group: In the emergency room, pitavastatin 4mg p.o. was administered to patients who were then immediately transferred to cathlab to undergo emergency coronary angiography (CAG) and PCI. After the procedure, all patients had long-term pitavastatin treatment 4mg/d.

2mg group: pitavastatin 2mg in the emergency room followed by 2mg once daily.

Dose and timing of anisodamine administration

2000ug group: Intracoronary administration of anisodamine 2000ug.
1000ug group: Intracoronary administration of anisodamine 1000ug.

The optimal timing of anisodamine administration: 1) initial TIMI grade > 0; or 2) initial TIMI grade = 0, but when the guidewire was advanced through the total occlusion to the distal site of the IRA, TIMI grade > 0; or 3) otherwise, over-the-wire (OTW) balloon catheter was introduced to the distal site of the IRA, then drugs were administered through OTW.

Above all, the study population was divided into four groups: Group A (pitavastatin 2mg and anisodamine 1000ug); Group B (pitavastatin 2mg and anisodamine 2000ug); Group C (pitavastatin 4mg and anisodamine 1000ug); Group D (pitavastatin 4mg and anisodamine 2000ug).

Other medications were administered to all the patients according to the current best clinical practice. Tirofiban administration was under the careful discretion of interventional cardiologists.

CAG and other examinations

Patients underwent CAG and PCI by transradial artery access. All the angiographic results (initial TIMI, final TIMI / CTFC / TMPG) were evaluated by two cardiologists blinded to the clinical status of the patient and the treatment modality.

Systolic, diastolic and mean coronary sinus pressures were determined by invasive catheterization before and 1 min, 5 min, 10 min after anisodamine administration.

Infarct size was estimated by peak levels of creatine kinase-MB (CK-MB) and troponin I (cTnI) which were determined before and every 4 h after the procedure.

A 18-lead ECG was recorded both on admission and at 90 min after PCI. ST-segment elevation was recorded in millimeters 20 ms after the J point. The sum of ST-segment elevation was calculated in leads II, III, aVF for inferior infarction. A decrease in the sum of ST-segment elevation by ≥ 70% was categorized as complete ST-segment resolution (STR) [9] and used as an indirect index of myocardial reperfusion after PCI [10].

Primary end point

The primary end point was the incidence of TMPG 3 after the procedure.

Major adverse cardiovascular events (MACEs)

Main adverse cardiac events (MACE): (1) cardiac death; (2) new myocardial infarction (MI); (3) target vessel revascularization (TVR). Composite endpoints were evaluated during the hospital stay and 30d after discharge.

Statistical analysis

At the climax of the PCI era, a reasonable estimate of the proportion of patients who get optimal myocardial reperfusion (TMPG 3), among those without cardiogenic shock undergoing PCI, is approximately 50%[1]. It is speculated that the proportion of postprocedural TMPG 3 can be up to 90% after high-dose anisodamine and pitavastatin administration. Accordingly, at least 26 patients per group were required for the power of the test set at 0.8 and statistical significance level (2-sided) at 0.05.

The continuous variables were recorded as means ± SD, and the categorical variables were presented as percentages. Continuous variables were compared using ANOVA and proportions were compared using chi-square test or Fisher's exact test. Multivariate logistic regression analysis was used to explore the possible factors associated with the optimal myocardial reperfusion (TMPG 3). For peak CK-MB and left ventricular ejection fraction (LVEF), factorial design ANOVA was applied to elucidate the main effects and interactions of the two drugs. *P* values of less than 0.05 were considered statistically significant. All calculations were computed with the aid of SPSS statistical software (version 16.0).

Results

Main demographic and clinical features

There were no significant differences in age, gender, past medical histories (hypertension, diabetes, current smokers, previous angina/MI/PCI) and basic medications among these four groups.

Procedural features

In these four groups, the IRA was dominantly RCA followed by LCX, while over half of the IRA showed thrombus score 3-4. After the procedure, the proportion of TMPG 3 was significantly higher in group D than that in other groups (p = 0.011); the proportions of postprocedural TIMI 3 and complete STR were the highest in group D, but no statistical differences were achieved, only a trend (p=0.073 and 0.051 respectively).

Main clinical index and follow up

The peak CK-MB and cTnI were the lowest and LVEF three days after the procedure was highest in group D. Anisodamine combined with pitavastatin had the synergistic effect in reducing the peak level of CK-MB with statistical significance (p = 0.001) while the synergistic effect trend in increasing LVEF without statistical significance (p = 0.284). Anisodamine elevated BP and HR, but except that one case appeared atrial premature beat in group B, no other severe tachyarrhythmias were observed during and after the procedure. The follow up during hospitalization and 30 days after discharge did not differ among these four groups.

Predictors of TMPG 3 by multivariate logistic analysis

The result displayed: thrombus score 3-4 and low diastolic blood pressure (DBP) before anisodamine were the independent risk factors for poor myocardial reperfusion (expressed as TMPG < 3), while anisodamine 2000ug before PCI was protective for optimal myocardial reperfusion after the procedure.

Discussion

The main findings of this study were as follows: 1) high-dose anisodamine and pitavastatin could improve TIMI blood flow and TMPG and promote complete STR after the procedure; 2) high-dose anisodamine and pitavastatin could remarkably decrease the levels of peak CK-MB and cTnI after the procedure, indicating that the size of myocardial infarction was decreased; 3) high-dose anisodamine and pitavastatin could significantly ameliorate the cardiac function represented as LVEF; 4) thrombus score 3-4 and low DBP before anisodamine were the independent risk factors for poor myocardial reperfusion, while anisodamine 2000ug before PCI was protective

for optimal myocardial reperfusion after the procedure; 5) intracoronary administration of anisodamine 2000ug was safe. In addition, anisodamine properly elevated BP and HR, increased the coronary perfusion pressure and finally ameliorated the myocardial reperfusion and clinical prognosis; 6) anisodamine and pitavastatin had cooperative interactions, and the efficacy of high-dose anisodamine and pitavastatin was superior to other combinations.

No-reflow is a multifactorial phenomenon with many pathological changes that eventually lead to microvascular damage and impaired myocardial perfusion [11-13]. The main factors that contribute to NR include: 1) Endothelial and myocardial cell edema damage the microvascular structure, which leads to microcirculatory compression and cell ischemia [12]; 2) Ischemia-reperfusion injury causes endothelial swelling, interstitial and intracellular edema and intraluminal microthrombi [13]. In addition, after reperfusion, the expression of adhesion molecules, activation of leukocytes, production of oxygen free radicals and release of vasoactive substances are remarkably increased, which may expand microvascular damage area; 3) Dysfunctional endothelium and the potent vasoconstrictors (serotonin, angiotensin II, endothelin-1) May result in microvascular spasm [14]; 4) Mechanical obstruction of leukocytes and their released products including oxygen free radicals, proteolytic enzymes and pro-inflammatory factors may contribute to tissue damage; 5) Microemboli consisting of thrombus fragments, blood cells aggregates, platelet plugs and atherosclerotic debris may obstruct microcirculation [15]; and 6) Extrinsic coagulation pathway activation [16].

The mechanisms of anisodamine in the prevention of NR and improvement of myocardial microcirculation might be multifactorial: 1) relieving the spasm of the conductive arteries, prearterioles, arterioles, and dredging coronary microcirculation; 2) restoring microvascular autonomic rhythm of tide-like perfusion [3] which is destroyed by NR; 3) increasing the coronary perfusion pressure by increasing blood pressure (especially the diastolic and mean blood pressure) and heart rate, which is very beneficial for the correction of NR and the improvement of coronary microcirculation; 4) inhibiting acetycholine receptor and regulating the rebalance between sympathetic and vagus nervous systems; 5) correcting hypotension and bradycardia and maintaining hemodynamic stabilization; 6) to some degree, anisodamine has the role similar to calcium channel antagonist. It can prevent intracellular calcium overload and attenuate the spasm of microcirculation; 7) inhibiting lipid superoxidation and oxygen free radicals formation, which lessens the injury of endothelial cells [17, 18]; 8) alleviating the oppression of myocardial swelling on microcirculation so as to improve the coronary antegrade blood flow [19].

LAMIS II trial [20] was designed to evaluate the efficacy and safety by different doses of pitavastatins in AMI patients. It suggested that although LDL-C was reduced more significantly by using 4 mg of pitavastatin compared to 2 mg of pitavastatin, the event rate was comparable. Our study showed that 4 mg of pitavastatin plus 2000ug of anisodamine could obviously improve myocardial reperfusion, and combinations of these two drugs had positive synergistic effect.

This study had some limitations. Firstly, this is a single-center, small-scale and short-term study, therefore, complete STR and MACE maybe had significant differences among these four groups in a future study with larger sample size and longer-time follow-up. Secondly, there were little researches concerning anisodamine, so the optimal dose range of anisodamine should be further explored. For example, anisodamine was administered 5000ug intracoronarily in our center.

Conclusion

High-dose anisodamine and pitavastatin combination can better ameliorate myocardial reperfusion and protect cardiac function in patients with AIMI undergoing primary PCI.

References

1. Niccoli G., *et al*. "Myocardial no-reflow in humans". *Journal of the American College of Cardiology* 54.4 (2009): 281-292.
2. Chan W., *et al.* "Usefulness of transient and persistent no reflow to predict adverse clinical outcomes following percutaneous coronary intervention". *American Journal of Cardiology* 109.4 (2012): 478-485.
3. Xiu RJ., *et al*. "Anisodamine inhibits thromboxane synthesis, granulocyte aggregation, and platelet aggregation. A possible mechanism for its efficacy in bacteremic shock". *JAMA* 247.10 (1982): 1458-1460.
4. Fu XH., *et al*. "Effect of intracoronary administration of anisodamine on slow reflow phenomenon following primary percutaneous coronary intervention in patients with acute myocardial infarction". *Chinese Medical Journal* 120.14 (2007): 1226-1231.
5. Wang YB., *et al*. "Safety and efficacy of anisodamine on prevention of contrast induced nephropathy in patients with acute coronary syndrome". *Chinese Medical Journal* 125.6 (2012): 1063-1067.
6. Wang Y., *et al*. "Protective effects of anisodamine on renal function in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention". *The Tohoku Journal of Experimental Medicine* 224.2 (2011): 91-97.
7. Geng W., *et al*. "Preventive effects of anisodamine against contrast-induced nephropathy in type 2 diabetics with renal insufficiency undergoing coronary angiography or angioplasty". *Chinese Medical Journal* 125.19 (2012): 3368-3372.
8. Zhang F., *et al*. "Effect of statins pretreatment on periprocedural myocardial infarction in patients undergoing percutaneous coronary intervention: a meta-analysis". *Annals of Medicine* 42.3 (2010): 171-177.
9. Shen J., *et al*. "Clinical benefits of adjunctive tirofiban therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention". *Coronary Artery Disease* 19.4 (2008): 271-277.
10. Huber K., *et al*. "Use of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention: insights from the APEX-AMI trial". *European Heart Journal* 31.14 (2010): 1708-1716.
11. Galiuto L. "Optimal therapeutic strategies in the setting of post-infarct no reflow: the need for a pathogenetic classification". *Heart* 90.2 (2004): 123-125.
12. Reffelmann T and Kloner RA. "The "no-reflow" phenomenon: basic science and clinical correlates". *Heart* 87.2 (2002): 162-168.
13. Kloner RA., *et al.* "Ultrastructural evidence of microvascular damage and myocardial cell injury after coronary artery occlusion: which comes first". *Circulation* 62.5 (1980): 945-952.
14. Niccoli G., *et al*. "Endothelin-1 and acute myocardial infarction: a no-reflow mediator after successful percutaneous myocardial revascularization". *European Heart Journal* 27.15 (2006): 1793-1798.
15. Topol EJ and Yadav JS. "Recognition of the importance of embolization in atherosclerotic vascular disease". *Circulation* 101.5 (2000): 570-580.
16. Zhao B., *et al*. "The role of von Willebrand factor and ADAMTS13 in the no-reflow phenomenon: after primary percutaneous coronary intervention". *Texas Heart Institute Journal* 38.5 (2011): 516-522.
17. Matsumoto H., *et al*. "Depletion of antioxidants is associated with no-reflow phenomenon in acute myocardial infarction". *Clinical Cardiology* 27.8 (2004): 466-470.
18. Reffelmann T., *et al*. "No-reflow phenomenon persists long-term after ischemia/reperfusion in the rat and predicts infarct expansion". *Circulation* 108.23 (2003): 2911-2917.
19. Zalewski J., *et al*. "Detection of microvascular injury by evaluating epicardial blood flow in early reperfusion following primary angioplasty". *International Journal of Cardiology* 96.3 (2004): 389-396.
20. Hong YJ., *et al*. "Efficacy and safety of pitavastatins in patients with acute myocardial infarction: Livalo in Acute Myocardial Infarction Study (LAMIS) II". *The Korean Journal of Internal Medicine* 32.4 (2017): 656-667.