

Effect of doxycycline and atorvastatin on improving exercise tolerance in patients with angina pectoris

Lei Song^{1**}, Guangmei Zou^{2**} and Xiaojun Wang^{1*}

¹Department of Geratology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University Medical College, Yantai, China

²Department of Cardiovascular Surgery, The Affiliated Yantai Yuhuangding Hospital of Qingdao University Medical College, Yantai, China

Abstract: The therapeutic effect of statins on the stabilization of atherosclerotic plaques has been affirmed. In recent years, the inhibition of matrix metalloproteinases (MMPS) of tetracycline drug doxycycline has attracted more and more attention. In this paper, we observed the effect of atorvastatin and doxycycline on exercise tolerance in patients with stable angina pectoris. The results showed that there was no significant difference in the clinical efficacy of the two groups and the effect on the exercise tolerance ($P < 0.05$). There were 4 cases of mild gastrointestinal reaction in the doxycycline group and no other serious adverse reactions. The total effective rate of treatment in the doxycycline group was 93.3%. Doxycycline treatment significantly reduced the frequency of angina pectoris and the incidence of cardiovascular events, and the treatment effect was better. To sum up, we think doxycycline is a safe, cheap, therapeutic drug to stabilize plaque.

Keywords: Atorvastatin, blood lipid level, atherosclerosis, doxycycline, matrix metalloproteinases.

INTRODUCTION

It is well known that lipid lowering drugs, antioxidants, receptor blockers and angiotensin converting enzyme inhibitors have been affirmed in the treatment strategies for stabilizing atherosclerotic plaques (Bobbi *et al.*, 2016). In recent years, through active exploration, we found that the inhibitory effect of tetracycline drug doxycycline on matrix metalloproteinases (MMPs) is attracting more and more attention (Dennis *et al.*, 2014; Galasso *et al.*, 2015). Doxycycline, as a broad-spectrum antibiotic, is a broad-spectrum antibiotic with rapid and complete absorption of the gastrointestinal tract (Claassen *et al.*, 2012). The plasma half-life is 15~25h, and the effective blood concentration is more than 24h, so only once a day is needed. Because of gastrointestinal reactions and other adverse reactions, so people used tetracyclines cautious (Espinel *et al.*, 2015). But in recent years, people's recognition is due to its clinical application as a MMPS inhibitor (Eugene *et al.*, 2017). At present, it is considered that MMP S is closely related to the plaque instability and the occurrence of acute coronary syndrome (Acs) in atherosclerosis (AS). Studies have shown that the endothelial cells of normal vascular wall can not secrete MMPS, and when AS occurs, local hypoxia, oxidized low density lipoprotein and serum leptin can induce MMPS in the endothelial cells in the surface of AS plaque and in the neovascular wall epithelium in the plaque (Fang *et al.*, 2017). Atorvastatin calcium is a statin drug that regulates lipid metabolism, anti platelet aggregation, inhibits atherosclerosis and improves myocardial ischemia (Emir *et al.*, 2014). When using statins, we should closely

monitor biochemical indicators such as aminotransferase and creatine kinase, and discover the liver damage and myopathy in time (Giulia *et al.*, 2016). We should pay more attention to monitoring the safety of drugs when we use intensive lipid-lowering therapy.

Statins and matrix metalloproteinases (MMPS) inhibitors can reduce the mortality and cardiovascular events in patients with coronary heart disease (CHD), but the effects of statins and doxycycline on myocardial ischemia in patients with normal stable angina pectoris are less reported (Beth *et al.*, 2012). In this paper, we observe the effect of atorvastatin and doxycycline on the clinical efficacy and the exercise tolerance in patients with normal stable angina pectoris, and evaluate the effect of atorvastatin and doxycycline on the treatment of myocardial ischemia in patients with stable angina.

MATERIALS AND METHODS

The subjects were patients with coronary heart disease and angina pectoris hospitalized in our hospital in 2016. Conforming to the following conditions: (1) patients with stable angina pectoris: squeezing or constrictive pain or discomfort caused by tiredness or precordial or precardiac region, can be relieved by rest or sublingual nitroglycerin tablets 5 min (Heer *et al.*, 2015); (2) coronary artery angiography was diagnosed as coronary heart disease; (3) patients with normal blood lipids (serum cholesterol (TC) < 5.72 mmol/L, triglyceride (TG) < 1.24 mmol/L and low density lipoprotein cholesterol (LDL-C) < 3.64 mmol/L). In the original routine drug treatment (aspirin, clopidogrel

*Corresponding author: e-mail: 18841526@qq.com

**Lei Song and Guangmei Zou contributed equally to this article

and other antiplatelet drugs mainly, angina pectoris attack with nitroglycerin to alleviate angina pectoris attack) unchanged condition, the active plate exercise test, the positive after 1wk exercise test again, the difference in the duration of the 2 exercise duration <10% angina as a stable type. Exclude the following patients: Myocardial infarction, unstable angina, percutaneous coronary angioplasty in 6 months, heart failure, cardiac arrest, valvular heart disease, severe arrhythmia, liver and kidney insufficiency, digitalis, β -receptor blocker, calcium antagonist or a long effect nitrate drug that can not be stopped.

A total of 150 subjects were selected, including 83 males, 67 females, average age as (52.4±7.1) years old. The random draw was divided into 2 groups, each with 75 cases. There were 41 males and 34 females in the Atorvastatin group, average age as (54.2±6.9) and the doxycycline group had 42 males and 33 females, with an average age as (57.1±8.2). There was no significant difference in gender, age, smoking, angina pectoris frequency and blood lipid level between the 2 groups ($P>0.05$). The study was approved by Ethics Committee of the Affiliated Yantai Yuhuangding Hospital of Qingdao University Medical College, approval number as 16YYHQUPD and all patients signed on the informed consent.

Therapeutic method

At the same time, the Atorvastatin group was treated with atorvastatin, 10mg every time, and lasted for 8 weeks. The doxycycline group was given 100mg with doxycycline each time. The oral administration was taken once a night for 8 weeks. When necessary, the two groups were treated with Nitroglycerin tablets.

Observation method

The frequency of angina pectoris and the dosage of nitroglycerin were recorded before and after treatment. The Marguette case15 treadmill was used as the treadmill exercise test, and the 12 lead electrocardiogram was monitored according to Bruse operation rules (Jacob *et al.*, 2016). The standard of exercise electrocardiogram is positive: after J point, the 0.08sST segment is horizontal or downward, and the downward displacement is more than 1mm. Before exercise, the ST segment descends, and it moves down more than 1mm on the original basis. Exercise for patients end point appear obvious weakness, shortness of breath, dyspnea, heart rate or the corresponding age limit.

The patient's exercise tolerance was measured, including the time required for movement to ST segment depression of 1mm, time required for movement to angina, and duration of movement, and (Σ ST) in the ST segment of the lead at the time of movement 6min.

STATISTICAL ANALYSIS

All data are counted by SPSS10.0 software package. Measurement data were expressed by mean \pm standard deviation. χ^2 test and t test were used for comparison between groups. Paired t test was used before and after treatment.

RESULTS

Clinical effect and effect on exercise tolerance

After 2 weeks of treatment for 8 weeks, the frequency of angina pectoris and the dosage of nitroglycerin decreased significantly ($P<0.01$). Σ ST decreased, the time required for exercise to ST segment depression 1mm, the time required for movement to angina pectoris, and duration of exercise were significantly prolonged ($P<0.01$). There was no significant difference between the 2 groups ($P>0.05$) (table 1).

Before treatment, blood lipids in two groups were in the normal range, but there was no significant difference in blood lipid level between the two groups. In atorvastatin group, TC, TG and LDL-C decreased ($P<0.01$) and HDL-C increased ($P<0.05$). There was no significant change in Doxycycline group ($P>0.05$). There was a significant difference between the 2 groups ($P<0.01$) (table 2).

Comparison of two groups of patients with ischemic related events

After clinical follow-up, the total ischemic related events in atorvastatin group were 25.3% (19/75), of which unstable angina was 16% (12/75), acute myocardial infarction was 2.6% (2/75), and sudden cardiac death was 1.3% (1/75); the total ischemic related events in the doxycycline group were 13.3% (10/75), unstable angina 12% (9/75) and acute myocardial infarction 1.3% (1/75). Sudden cardiac death was 2.6% (2/75). There was no significant difference in the total ischemia related events between the two groups ($P>0.05$). The effect of the treatment is shown in table 3.

Adverse reaction

The adverse reaction is shown in table 4. There was no serious adverse reaction in the 2 groups. There were 1 cases of skin pruritus in statin treatment group, but they were tolerable. 4 cases of mild gastrointestinal reactions occurred in Doxycycline group. The 2 groups had no abnormal changes in liver and kidney function and no serious muscle toxicity. No muscle enzyme increased.

DISCUSSION

In this study, the number of angina pectoris episodes, the dosage of nitroglycerin decreased significantly, myocardial ischemia was reduced, and the exercise

Table 1: The clinical efficacy of atorvastatin and doxycycline

Factor	Doxycycline group		Atorvastatin group	
	Before treatment	After treatment	Before treatment	After treatment
Times per week / times of angina pectoris	8.0±2.4	4.2±1.7	7.6±2.8	3.5±1.2
The consumption of nitroglycerin /mg ·WK ⁻¹	27.6±5.8	11.5±2.5	30.2±4.9	12.3±2.6
Motion duration /s	397.0±20.2	459.0±25.4	385.0±21.6	447.2±22.3
The time required for the ST segment /s	312.6±8.4	426.8±14.1	295.3±9.5	451.6±15.8
Time required for exercise to angina pectoris /s	246.3±9.3	452.1±12.8	225.6±8.7	441.3±13.4
Σ ST/min	7.9±2.5	5.2±1.3	8.4±2.4	5.1±1.2
Resting heart rate and systolic pressure	9935±2105	9948±2247	9950±2194	9964±2203
Heart rate and systolic pressure in maximum exercise	24094±3150	24182±3208	33481±3135	33672±3024

Table 2: The effect of atorvastatin and doxycycline on blood lipid

Factor	Doxycycline group		Atorvastatin group	
	Before treatment	After treatment	Before treatment	After treatment
Total cholesterol	5.1±1.2	5.6±1.3	5.2±1.5	4.7±0.9
Three acyl glycerol	1.65±0.25	1.71±0.27	1.69±0.28	1.45±0.13
High density lipoprotein cholesterol	1.47±0.15	1.42±0.13	1.42±0.18	1.55±0.20
Low density lipoprotein cholesterol	3.35±0.34	3.51±0.38	3.42±0.38	3.19±0.47

Table 3: Treatment effect

Group	Obviously effective	Partial validity	Invalid	Total effective rate
Doxycycline group	38	32	5	93.3%
Atorvastatin group	35	37	3	96.0%

Table 4: Adverse reaction

Group	Skin Itch	Gastrointestinal reaction	Abnormal function of liver and kidney	Myocal reaction
Doxycycline group	0	4	0	0
Atorvastatin group	1	2	0	0

tolerance was significantly improved (Mannen *et al.*, 2010). Atorvastatin could improve myocardial ischemia and exercise tolerance. However, it did not affect the product of heart rate and blood pressure, suggesting that it did not reduce the heart rate (Nishida *et al.*, 2015). The amount of muscle oxygen consumption is not related to the decrease of oxygen consumption, which may be related to the effect of lipid regulation or beyond (Perl *et al.*, 2015). Statins can further reduce normal blood lipid levels, still help delay and reverse atherosclerosis and reduce mortality and ischemia related events. Studies have shown that LDL-C decreased 1mmol/L, and the major cardiovascular events decreased by 25% (Presbitero *et al.*, 2003; Sanomura *et al.*, 2014). In addition to lipid regulation, statins also participate in antioxidant, anti-inflammatory or down-regulation of angiotensin - II receptor, inhibit some of the coagulation factors, the process of atherosclerosis, and promote collagen formation (Samar *et al.*, 2017). Statins can adjust endothelial function, stabilize or even narrow the

atherosclerotic plaque, thereby indirectly improve the symptoms of myocardial ischemia, reduce the events of coronary heart disease, and reduce the mortality of coronary heart disease.

Doxycycline can also improve myocardial ischemia related symptoms in patients with coronary heart disease and improve exercise tolerance, which is related to the stability of atherosclerotic plaque with doxycycline as a matrix metalloproteinase inhibitor (MMPs) inhibitor (Solinas *et al.*, 2015). MMPs is closely related to the instability of atherosclerotic plaque and the occurrence of acute coronary syndrome (ACS). Macrophages secrete a variety of MMPs in atherosclerotic plaque, and the matrix degradation activity of the atheromatous plaque (that is, plaque fiber cap and the basal junction) increases greatly, and the plaque is vulnerable to rupture (Singh *et al.*, 2016). Doxycycline inhibits its function by combining the two valence cations of leukocyte, thus inhibiting the aggregation of neutrophils and macrophages and

inhibiting the activity of MMPs, thus stabilizing plaque, reducing thrombosis and improving myocardial ischemia. Nitrate esters are often poorly tolerated due to dilated blood vessels, headache and heart rate (Sanomura *et al.*, 2014; Vagnarelli *et al.*, 2015). Doxycycline and atorvastatin do not affect the blood flow of the coronary arteries, but also have no adverse effects of nitrates, well tolerated, combined with the nitric esters that affect hemodynamics and their complementary effects can improve the efficacy of anti angina. Not only that, it can also reduce the incidence of coronary heart disease, reduce the mortality of coronary heart disease, and improve the prognosis.

The non lipid lowering effect of statins is the main mechanism affecting motor function (Khera *et al.*, 2015). Although the non lipid-lowering effect of statins has many beneficial functions, such as anti inflammation and improvement of endothelium, it has a negative effect on exercise function, which does not seem to be consistent with the conclusion that most clinical studies do not affect exercise (Li *et al.*, 2015). Besides the protective effect of statins on cardiac myocytes, the influence of multiple confounding factors may be the key to explain this phenomenon (Lv *et al.*, 2015). The adverse effects of exercise after taking statins are affected by a variety of risk factors, including the nature of the drug itself, and related to the patient's own factors and the history of drug use. Therefore, clinicians should be familiar with the properties and standard dosage of statins in the process of statins, and carefully collect the patient's history of disease and drug use, which is of great significance to avoid the adverse effects of statins in the application of statins.

CONCLUSION

The group received oral doxycycline for 8 weeks, and no serious adverse reactions were found. Only a few patients had mild gastrointestinal discomfort, but they still tolerated. The current dose of doxycycline is still controversial. This study aimed to improve the effect of doxycycline on improving the symptoms of coronary heart disease, and no significant side effects occurred. Doxycycline treatment significantly reduced the frequency of angina pectoris and the incidence of cardiovascular events and the treatment effect was better. To sum up, we think that doxycycline is a highly safe, long time service, and cheap, promising non selective inhibition of MMPS synthesis and activation of therapeutic drugs with stable plaques, worthy of clinical attention. At the same time, when using the doxycycline hydrochloric acid tablets, the pharmacists should closely observe the adverse reactions. Once they occur, they should immediately discontinue the medication and take symptomatic treatment measures.

ACKNOWLEDGEMENTS

Authors are thankful for the support from The Affiliated Yantai Yuhuangding Hospital of Qingdao University Medical College.

REFERENCES

- Beth A, Amanda L, Jeffrey A, Kevin D, Christopher T and Aaron L (2012). Effect of Statins on Creatine Kinase Levels Before and After a Marathon Run. *The Amer. J. Card.*, **109**(2): 282-287.
- Bobbi S, Paul S, Diep K, David F, Laurel B, Jeffrey P, Elizabeth S, Lynne M, Martin E and Adam J (2016). Identification of a novel pathogenic *Borrelia* species causing Lyme borreliosis with unusually high spirochaetemia: A descriptive study. *The Lanc. Infect. Disea.*, **16**(5): 556-564.
- Claassen M, Sybrandy KC, Appelman YE and Asselbergs FW (2012). Gender gap in acute coronary heart disease: Myth or reality? *World J. Cardiol.*, **4**(2): 36-47.
- Dennis J, Celeste T, Jonathan KE, Matthew A, Kyle B, John R and Meghan S (2014). Cardiac Rehabilitation Improves Functional Capacity and Patient-Reported Health Status in Patients With Continuous-Flow Left Ventricular Assist Devices: The Rehab-VAD Randomized Controlled Trial. *JACC: Hea. Fail.*, **2**(6): 653-659.
- Emir S, Sozen S, Bali I, Gurdal SO, Turan BC, Yıldırım O and Yetisyigit T (2014). Outcome analysis of laparoscopic D1 and D2 dissection in patients 70 years and older with gastric cancer. *Int. J. Clin. Exp. Med.*, **7**(10): 3501-3511.
- Espinel J, Pinedo E, Ojeda V and Del Rio MG (2015). Treatment modalities for early gastric cancer. *World J. Gastrointest. Endosc.*, **7**(12): 1062-1069.
- Eugene D Shapiro, Gary P Wormser (2017). Prophylaxis with topical azithromycin against Lyme borreliosis. *The Lanc. Infect. Dise.*, **17**(3): 246-248.
- Fang W and Ruan W (2017). Advances in uniportal video-assisted thoracoscopic surgery for non-small cell lung cancer. *Minim Invasive Surg. Oncol.*, **1**(1): 20-30.
- Galasso G, Savonitto S and Piccolo R (2015). Effect of an invasive strategy on outcome in patients ≥ 75 years of age with non-ST-elevation acute coronary syndrome. *Am. J. Cardiol.*, **115**(5): 576-580.
- Giulia M, Michela D, Elena C, Antonella L, Kejla M, Maria C and Adriano F (2016). Statin-induced myotoxicity is exacerbated by aging: A biophysical and molecular biology study in rats treated with atorvastatin. *Toxic. and Appl. Pharm.*, **306**: 36-46.
- Heer T, Hochadel M and Schmidt K (2015). Gender differences in therapeutic recommendation after diagnostic coronary angiography: Insights from the Coronary Angiography and PCI Registry of the German Society of Cardiology. *Clin. Res. Cardiol.*,

- 104**(6): 507-517.
- Jack C and Maria E (2011). Clinical studies on the management of periodontal diseases utilizing sub antimicrobial dose doxycycline (SDD). *Pharm. Res.*, **63**(2): 114-120.
- Jacob P, Allison D, Phillip J, Mona F, Eric S, Jerome L, Lawton S, Steven J and Dalane W(2016). Statins and Exercise Training Response in Heart Failure Patients: Insights From HF-ACTION. *JACC: Hea. Fail.*, **4**(8): 617-624.
- Khera S, Kolte D and Gupta T (2015). Temporal Trends and Sex Differences in Revascularization and Outcomes of ST-Segment Elevation Myocardial Infarction in Younger Adults in the United States. *J. Am. Coll. Cardiol.*, **66**(18): 1961-72.
- Li B, Liu HY, Guo SH, Sun P, Gong FM and Jia BQ (2015). Microsatellite instability of gastric cancer and precancerous lesions. *Int. J. Clin. Exp. Med.*, **8**(11): 21138-21144.
- Lv X, Zhang L, Huang R and Song W (2015). A clinical exploration of neoadjuvant chemotherapy with tegafur, gimeracil, and oteracil potassium capsules combined with oxaliplatin for advanced gastric cancer. *Int. J. Clin. Exp. Med.*, **8**(10): 19030-19036.
- Mannen K, Tsunada S and Hara M (2010). Risk factors for complications of endoscopic submucosal dissection in gastric tumors: Analysis of 478 lesions. *J Gastroenterol*, **45**(1): 30-36.
- Nishida T, Kato M, Yoshio T, Akasaka T, Yoshioka T, Michida T, Yamamoto M, Hayashi S, Hayashi Y, Tsujii M and Takehara T (2015). Endoscopic submucosal dissection in early gastric cancer in elderly patients and comorbid conditions. *World J. Gastrointest. Endosc.*, **7**(5): 524-531.
- Perl L, Bental T, Assali A, Vaknin-Assa H, Lev E, Kornowski R and Porter A (2015). Impact of female sex on long-term acute coronary syndrome outcomes. *Coron. Artery Dis.*, **26**(1): 11-16.
- Presbitero P and Carcagnì A (2003). Gender differences in the outcome of interventional cardiac procedures. *Ital. Heart J.*, **4**(8): 522-527.
- Samar O, Ahmed E, Dina A, Mahmoud M, Mahmoud M and Aiman S (2017). Rosuvastatin safety: An experimental study of myotoxic effects and mitochondrial alterations in rats. *Toxic. Lett.*, **265**: 23-29.
- Sanomura Y, Oka S and Tanaka S (2014). Continued use of low-dose aspirin does not increase the risk of bleeding during or after endoscopic submucosal dissection for early cancer. *Gastric Cancer*, **17**(3): 489-496.
- Singh DP, Singh SS, Singh S, Shrivastava AK and Sinha K (2016). Clinical profile of acute coronary syndrome (ACS) in young adults of North Indian population. *J. Assoc. Physicians India*, **64**(1): 33.
- Solinas E, Vignali L and Ortolani P (2015). Association of bleeding, mortality and sex in acute coronary syndromes: the missing triangle. *J. Cardiovasc. Med. (Hagerstown)*, **16**(5): 347-354.
- Vagnarelli F, Taglieri N and Ortolani P (2015). Long-term outcomes and causes of death after acute coronary syndrome in patients in the Bologna, Italy, area. *Am. J. Cardiol.*, **115**(2): 171-177.