Tropical Journal of Pharmaceutical Research December 2023; 22 (12): 2505-2510
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v22i12.12

Original Research Article

Pitavastatin calcium significantly improves glucose and lipid metabolism of patients with coronary atherosclerosis and reduces the occurrence of adverse cardiovascular events

Jun Liu[1], Bing Li[2], Cuiping Wang[1]*
[1]Department of Cardiology, Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu Province, [2]Department of Cardiology, The Second Affiliated Hospital of Soochow University, Soochow, China

For correspondence: **Email: liujunlw111@163.com*

Sent for review: 17 July 2023 *Revised accepted: 3 December 2023*

Abstract

Purpose: *To determine the efficacy of pitavastatin calcium and atorvastatin calcium on coronary atherosclerosis (CA) and compare the influence of the two schemes on adverse cardiovascular events.*
Methods: *The medical records of 198 patients with CA admitted at Affiliated Hospital of Jiangsu University, China from August 2019 to May 2011 were analyzed retrospectively. The patients were grouped into pitavastatin calcium group (n = 102) and atorvastatin calcium group (n = 96). The efficacy, incidence of adverse cardiovascular events, as well as changes in blood lipid metabolism and blood glucose metabolism indices before and after therapy were recorded and compared.*
Results: *Compared with atorvastatin calcium group, pitavastatin calcium group yielded a significantly higher overall response rate (ORR, $p < 0.05$) and presented a significantly lower total incidence of cardiovascular adverse events ($p < 0.05$). After therapy, pitavastatin calcium group displayed significantly lower triglyceride, total cholesterol and low-density lipoprotein-cholesterol levels ($p < 0.05$), and also presented significantly higher high-density lipoprotein-cholesterol levels ($p < 0.05$) in contrast to atorvastatin calcium group. Furthermore, pitavastatin calcium group presented significantly lower fasting blood glucose and glycosylated hemoglobin levels than atorvastatin calcium group ($p < 0.05$).*
Conclusion: *Compared with atorvastatin calcium, pitavastatin calcium displays a better therapeutic effect in patients with CA, lowers the incidence of adverse cardiovascular events and improves glucose and lipid metabolism of patients. Future studies will focus on longer follow-up sessions to better understand the impact of the drugs on patient's prognosis.*

Keywords: *Pitavastatin calcium, Atorvastatin calcium, Coronary atherosclerosis, Adverse cardiovascular events*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Atherosclerosis is the most frequently diagnosed potential lesion of peripheral artery disease (PAD), coronary artery disease (CAD) as well as cerebrovascular disease [1]. When lipid deposition occurs in the inner wall of coronary artery and plaque is formed, the lumen of coronary artery narrows with gradual increase of the plaque, resulting in insufficient blood supply

to the myocardium, which in turn leads to a sudden drop in coronary blood flow, followed by myocardial ischemia and hypoxia in the controlled area. This is the etiology of coronary heart disease (CHD) [2]. At present, CHD accounts for about 45 % of all cardiovascular disease cases [3].

Atorvastatin calcium and pitavastatin calcium are frequently adopted statins in the therapy of CHD. Statins inhibit the formation and progression of plaques by reducing intravascular lipid deposition and plaque stability. However, different statins have diverse effects on patients with CHD [4]. Studies have shown that atorvastatin worsens diabetes mellitus, so its role in regulating blood glucose metabolism is controversial [5]. As a new generation of statins, pitavastatin substantially lowers total cholesterol (TC) as well as low-density lipoprotein-cholesterol (LDL-C) levels. In addition, it possesses a long half-life and high bioavailability [6].

At present, the effect of pitavastatin calcium and atorvastatin calcium on glucose and lipid metabolism in CHD patients is rarely studied and compared. Accordingly, this retrospective study compared the therapeutic results of pitavastatin calcium and atorvastatin calcium in the therapy of CHD.

METHODS

Patient data

The medical records of 198 CA patients admitted at the Affiliated Hospital of Jiangsu University, China between August 2019 and May 2021 were retrospectively analyzed. The patients were assigned to a pitavastatin calcium group (n = 102) or atorvastatin calcium group (n = 96). The study was performed with permission from the Medical Ethics Committee of the Affiliated Hospital of Jiangsu University (approval no. 20110315) and it met the criteria in the Declaration of Helsinki [7].

Inclusion and exclusion criteria

Inclusion criteria

The following category of patients were included in the study – patients who were diagnosed with moderate stenosis or more severe stenosis by coronary CT angiography and had more than 50 % vascular stenosis according to coronary angiography; patients who did not receive any statin treatment during the last 3 months before admission; as well as patients that had complete medical records.

Exclusion criteria

Patients were excluded from the study based on the following criteria – were allergic to the drugs adopted in this research; had suffered kidney and liver function injury; had poor compliance with the treatment scheme; suffered other malignant tumors within the same period; pregnant patients.

Therapeutic regimen

Each patient in pitavastatin calcium group was orally treated with 2 mg pitavastatin calcium once daily before bedtime. Each patient in atorvastatin calcium group was orally treated with 10 mg of atorvastatin calcium once daily before bedtime. The treatment cycle lasted for 3 months.

Criteria for efficacy evaluation

The efficacy in the two groups was evaluated after three months of treatment according to the following criteria:

Markedly effective (ME)*:* The electrocardiogram result was normal and the frequency of angina pectoris per week was $^1/_5$ of that before treatment; *Effective* (E)*:* The electrocardiogram result was normal and the frequency of angina pectoris per week was $^1/_5$ – $^1/_2$ of that before treatment; *Ineffective*: The electrocardiogram result was not improved or aggravated as compared with those before treatment [8]. Overall response rate (R) was calculated using Eq 1.

$$R = ME+E \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

Evaluation of parameters/indices

Primary outcome

The overall response rate among patients after therapy was compared. In addition, the adverse cardiovascular events in the two groups, within 6 months after therapy, were counted.

Secondary outcome

Blood lipid and blood glucose indices

The blood lipid indices and blood glucose indices of the two groups were compared before and after therapy. Fasting venous blood (3 mL) was acquired from each patient before and after therapy and then triglyceride (TG), LDL-C, high-density lipoprotein-cholesterol (HDL-C), TC as well as glycosylated hemoglobin (HbA1c) were

determined using an automatic biochemical analyzer (Labotronics, UK).

Statistical analysis

SPSS 20.0 (SPSS Co. Ltd, Chicago, USA) was used for statistical processing of acquired data, and GraphPad Prism 7 (GraphPad Software Co. Ltd, San Diego, USA) for data visualization into required Figures. Counting data were described as rate (%), analyzed through Chi-square test and expressed by χ^2. Measurement data were described as mean ± standard deviation (SD). All measurement data were normally distributed. The inter-group comparison of measurement data was conducted using the independent samples t-test, and their intro-group comparison was conducted using the paired t-test. Values of $p < 0.05$ indicate significant difference.

RESULTS

Baseline data

The two groups did not differ significantly in sex, age, course of disease, comorbid hypertension, body mass index (BMI), smoking history, comorbid hyperlipidemia, left ventricular end-diastolic dimension (LVDd), comorbid diabetes as well as left ventricular ejection fraction (LVEF) ($p > 0.05$, Table 1).

Efficacy

Pitavastatin calcium group yielded a significantly better overall response rate than atorvastatin calcium group (94.12 % *vs* 83.33 %, $p < 0.05$, Table 2).

Table 1: Baseline data in both groups

Parameter	Sub-item	Pitavastatin calcium group	Atorvastatin calcium group	χ^2/t	*P*-value
Age				1.077	0.299
	≥60 years	72 (70.59)	74 (77.08)		
	<60 years	30 (29.41)	22 (22.92)		
Gender				0.257	0.613
	Male	61 (59.80)	54 (56.25)		
	Female	41 (40.20)	42 (43.75)		
BMI				0.972	0.324
	≥25kg/m^2	42 (41.18)	33 (34.38)		
	<25kg/m^2	60 (58.82)	63 (65.63)		
Course of disease				0.551	0.458
	≥1 year	27 (26.47)	30 (31.25)		
	<1 year	75 (73.53)	66 (68.75)		
Smoking history				0.359	0.549
	Yes	31 (30.39)	33 (34.38)		
	No	71 (69.61)	63 (65.63)		
Comorbid hypertension				0.236	0.627
	Yes	64 (62.75)	57 (59.38)		
	No	38 (37.25)	39 (40.63)		
Comorbid hyperlipidemia				0.641	0.423
	Yes	90 (88.24)	88 (91.67)		
	No	12 (11.76)	8 (8.33)		
Comorbid diabetes				1.116	0.291
	Yes	26 (25.49)	31 (32.29)		
	No	76 (74.51)	65 (67.71)		
LVDd (mm)		56.77±3.22	57.25±3.32	1.033	0.303
LVEF (%)		46.70±2.29	46.29±2.10	1.063	0.289

Table 2: Efficacy comparison between both groups

Parameter	Pitavastatin calcium group	Atorvastatin calcium group	χ^2	*P*-value
Markedly effective	72 (70.59)	49 (51.04)		
Effective	24 (23.53)	31 (32.29)		
Ineffective	6 (5.88)	16 (16.67)		
Total effectiveness	96 (94.12)	80 (83.33)	5.824	0.016

Table 3: Adverse cardiovascular events in both groups

Parameter	Pitavastatin calcium group	Atorvastatin calcium group	χ^2	*P*-value
Angina pectoris	3 (2.94)	7 (7.29)		
Arrhythmia	3 (2.94)	6 (6.25)		
Myocardial infarction	1 (0.98)	3 (3.13)		
Total cardiovascular adverse events	7 (6.86)	16 (16.67)	4.630	0.031

Adverse cardiovascular events

In contrast to atorvastatin calcium group, pitavastatin calcium group presented a significantly lower total incidence of cardiovascular adverse events ($p < 0.05$, Table 3).

Blood lipid metabolism

Before treatment, the two groups did not differ significantly in TC, TG, LDL-C as well as ($p > 0.05$). Post-treatment, the TC, TG and LDL-C in both groups reduced significantly ($p < 0.05$), while the HDL-C levels were significantly elevated ($p < 0.05$), with significantly lower levels of TC, TG and LDL-C as well as significantly higher levels of HDL-C in pitavastatin calcium group ($p < 0.05$, Figure 1).

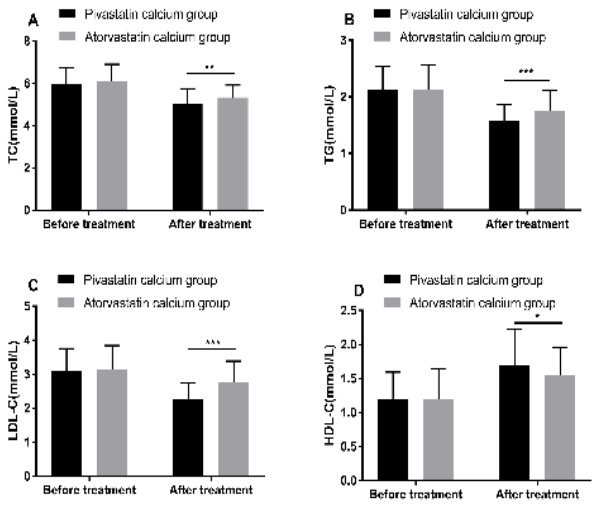

Figure 1: Changes in blood lipid metabolism before and after treatment. The levels of TC (A), TG (B), LDL-C (C) and HDL-C (D) in the two groups were compared before and after treatment. *$P < 0.05$ compared to the pre-treatment levels

Blood glucose metabolism

Pitavastatin calcium group presented significantly lowered HbA1c and fasting blood glucose levels than atorvastatin calcium group after treatment ($p < 0.05$, Figure 2).

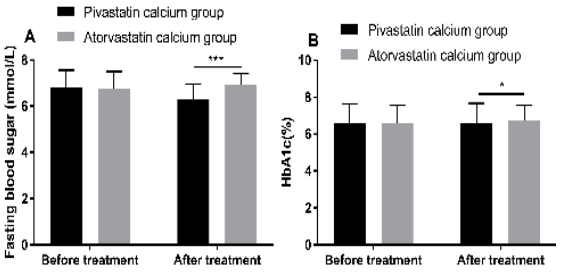

Figure 2: Changes in glucose metabolism indices before and after treatment. The levels of fasting blood sugar (A) and HbA1c (B) in the two groups were compared before and after treatment. *$P < 0.05$ compared to the pre-treatment levels

DISCUSSION

The prevention and treatment of atherosclerosis is crucial to the prevention of CHD. Dyslipidemia and inflammation are primary risk factors for atherosclerosis, and the increases in TC, TG as well as LDL-C and decrease in HDL-C are important independent risk factors for cardiovascular and cerebrovascular events including CHD, hypertension and cerebrovascular diseases [9]. Statins play a significant role in the prevention and treatment of atherosclerosis and perform several pivotal functions such as fighting against inflammation, improving vascular endothelial function, inhibiting the proliferation and migration of smooth muscle cells, resisting platelet aggregation, reducing thrombosis and inhibiting ventricular remodeling after myocardial infarction, as well as improving left ventricular function [10]. Atorvastatin inhibits platelet aggregation and thrombosis, improves vascular endothelial function, production of nitric oxide (NO) and microcirculation in treating myocardial infarction. It inhibits the synthesis of TC in the liver by suppressing the activity of HMG-CoA reductase in plasma and finally reduces the serum cholesterol concentration [11]. Atorvastatin also increases receptors on the surface of LDL cells in hepatocytes, thus increasing the uptake and decomposition of LDL, reducing its adhesion and damage to vascular endothelium and inhibiting the secretion of inflammatory transmitters, thereby improving the

function of vascular endothelium [12]. As a new generation of statins, pitavastatin directly regulates blood lipids and also functions in lowering LDL-C levels, promoting endothelial angiogenesis, improving endothelial function, stabilizing plaque, regulating immunity, resisting inflammation and oxidant stress and so on [13].

In this study, pitavastatin calcium group yielded a significantly higher overall response rate than atorvastatin calcium group (94.12 % *vs* 83.33 %) and presented a significantly lower total incidence of adverse cardiovascular events. Atorvastatin is metabolized mainly through cytochrome P450 isoenzyme CYP3A4 pathway, while pitavastatin is rarely metabolized *in vivo*. Many drugs used in cardiovascular, respiratory, digestive and endocrine systems are also metabolized through the CYP3A4 pathway. These drugs may interfere with the lipid-regulating property of atorvastatin or vice versa. When pitavastatin is metabolized in the liver through enterohepatic circulation, only a very small part of it is metabolized by CYP2C9, which does not affect the activity of CYP2C9 [14]. According to some studies, because of its cyclopropyl structure, pitavastatin has a stronger effect on enzymes, which is 5.7 times that of atorvastatin, and due to hepatocyte selectivity, it is rarely affected by metabolism and is well absorbed. In addition, it reaches the peak plasma concentration within 1 or 2 hr after oral administration, with an oral bioavailability of 51 % - 60%, so its curative effect is more lasting [15].

This study has also found that after treatment, the two statins substantially lowered the levels of TC, TG as well as LDL-C and elevated HDL-C levels. Additionally, after treatment, in contrast to atorvastatin calcium group, pitavastatin calcium group presented significantly lower TC, TG and LDL-C and significantly higher HDL-C. This suggests a better effect of pitavastatin calcium on improving and regulating lipid metabolism than atorvastatin calcium. Chan *et al*. [16] revealed that 4 mg of pitavastatin calcium reduces LDL-C by about 40 – 49 %, which is equivalent to 20 mg of atorvastatin [16].

It is still controversial whether statins increase the risk of abnormal glucose metabolism and diabetes mellitus, especially the risk of new-onset diabetes mellitus [17]. The glucose metabolism of patients was evaluated before and after treatment in this study. Pitavastatin calcium did not significantly give rise to blood glucose fluctuation compared with atorvastatin calcium, and even reduced blood glucose to some extent. This result is consistent with the report of Wang and co-workers which revealed that pitavastatin calcium more strongly improves patients' blood glucose than atorvastatin [18].

Limitations of this study

This study has some limitations. Firstly, the number of patients enrolled is limited, Secondly, as a retrospective study, this study also has some unavoidable bias. Finally, due to the limited time of inclusion, the long-term prognosis of patients is not completely clear.

CONCLUSION

Compared with atorvastatin calcium, pitavastatin calcium provides better efficacy in patients with CA. Pitavastatin calcium also lowers the incidence of adverse cardiovascular events and improves glucose and lipid metabolism in patients, thus enhancing efficacy. A future study with an increased sample size will be conducted to validate the findings.

DECLARATIONS

Acknowledgements

None provided.

Funding/Sponsorship

None provided.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Jun Liu and Bing Li conceived and designed the study and drafted the manuscript. Jun Liu and Cuiping Wang collected, analyzed and interpreted the experimental data. All authors revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethical Approval

This study was approved by the Ethics Committee of Lujiang County People's Hospital of Anhui Province (approval no. 52783521).

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Use of Artificial Intelligence/Large Language Models

None provided.

Use of Research Reporting Tools

None provided.

Open Access

REFERENCES

1. *Zhao S, Xu H, Liu F, Guo X, Zhang Y. Application of early multi-dimensional cardiac rehabilitation nursing in percutaneous coronary intervention and its effects on adverse events and patients' adherence to medication. J Mod Nurs Pract Res 2022; 2: 16. https://doi.org/10.53964/jmnpr.2022016*
2. *Ma J, Chen X. Anti-inflammatory therapy for coronary atherosclerotic heart disease: unanswered questions behind existing successes. Front Cardiovasc Med 2020; 7: 631398.*
3. *Aengevaeren VL, Mosterd A, Sharma S, Prakken NHJ, Möhlenkamp S, Thompson PD, Velthuis BK, Eijsvogels TMH. Exercise and coronary atherosclerosis: observations, explanations, relevance, and clinical management. Circulation 2020; 141: 1338-1350.*
4. *Henein MY, Vancheri S, Longo G, Vancheri F. The role of inflammation in cardiovascular disease. Int J Mol Sci 2022; 23(21): 12906. doi: 10.3390/ijms232112906.*
5. *Hirota T, Fujita Y, Ieiri I. An updated review of pharmacokinetic drug interactions and pharmacogenetics of statins. Expert Opin Drug Metab Toxicol 2020; 16: 809-822.*
6. *Zhang X, Xing L, Jia X, Pang X, Xiang Q, Zhao X, Ma L, Liu Z, Hu K, Wang Z, et al. Comparative lipid-lowering/increasing efficacy of 7 statins in patients with dyslipidemia, cardiovascular diseases, or diabetes mellitus: systematic review and network meta-analyses of 50 randomized controlled trials. Cardiovasc Ther 2020; 2020: 3987065. doi: 10.1155/2020/3987065.*
7. *World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310: 2191-2194.*
8. *Gao J, Wang X, Li L, Zhang H, He R, Han B, Li Z. Block matching pyramid algorithm-based analysis on the efficacy of Shexiang Baoxin pills guided by echocardiogram (ECG) on patients with angina pectoris in coronary heart disease. J Healthc Eng 2021; 2021:3819900.*
9. *Manduteanu I, Simionescu M. Inflammation in atherosclerosis: a cause or a result of vascular disorders? J Cell Mol Med 2012; 16: 1978-90.*
10. *Guan ZW, Wu KR, Li R, Yin Y, Li XL, Zhang SF, Li Y. Pharmacogenetics of statins treatment: Efficacy and safety. J Clin Pharm Ther 2019; 44: 858-867.*
11. *Balasubramanian R, Maideen NMP. HMG-CoA Reductase Inhibitors (Statins) and their Drug Interactions Involving CYP Enzymes, P-glycoprotein and OATP Transporters-An Overview. Curr Drug Metab 2021; 22: 328-341.*
12. *Tian X, Xiong Q, Chen L, Wen JR, Ru Q. Intervention of Catalpol on High-fat Diet-Induced Nonalcoholic Fatty Liver Disease in Mice. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2019; 41: 746-755.*
13. *Fici F, Faikoglu G, Tarim BA, Robles NR, Tsioufis K, Grassi G, Gungor B. Pitavastatin: Coronary atherosclerotic plaques changes and cardiovascular prevention. High Blood Press Cardiovasc Prev 2022; 29: 137-144.*
14. *Cooper-DeHoff RM, Niemi M, Ramsey LB, Luzum JA, Tarkiainen EK, Straka RJ, Gong L, Tuteja S, Wilke RA, Wadelius M, et al. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and statin-associated musculoskeletal symptoms. Clin Pharmacol Ther 2022; 111: 1007-1021.*
15. *Barrios V, Escobar C. Clinical benefits of pitavastatin: focus on patients with diabetes or at risk of developing diabetes. Future Cardiol 2016; 12: 449-466.*
16. *Chan P, Shao L, Tomlinson B, Zhang Y, Liu ZM. An evaluation of pitavastatin for the treatment of hypercholesterolemia. Expert Opin Pharmacother 2019; 20: 103-113.*
17. *Zhang Y, You X, Ren Y, Cui J. Implications of statin metabolism-related gene testing in guiding individualized drug use in cardiovascular diseases. Trop J Pharm Res 2023; 22: 447-452.*
18. *Wang YB, Fu XH, Gu XS, Fan WZ, Jiang YF, Hao GZ, Miao Q, Cao J, Fu B, Li Y. Effects of intensive pitavastatin therapy on glucose control in patients with non-ST elevation acute coronary syndrome. Am J Cardiovasc Dis 2017; 7: 89-96.*