Comparison and analysis of the therapeutic effect of different statins in the treatment of atherosclerosis

Meifeng Liu[1], Guiting Liu[2*] and Meiying Wang[3]
[1]Changyi people's Hospital, Internal Medicine-Neurology, Changyi, China
[2]Changyi people's Hospital, Pediatrics, Changyi, China
[3]Changyi people's Hospital, Disinfection Supply Center, Changyi, China

Abstract: Studies have confirmed that lipid-lowering drugs can effectively control the morbidity and mortality of cardiovascular and cerebrovascular diseases and statins are the most widely used. The aim of this study is to investigate the effect and mechanism of different statins on atherosclerotic patients. The patients were randomly divided into 4 groups according to the digital method, and the patients were treated with conventional therapy, simvastatin treatment, pravastatin treatment, atorvastatin treatment. It is concluded that statins are safe, effective and reliable for the treatment of atherosclerosis, and worthy of clinical promotion. The results also showed that after 6 months of taking statins, the levels of NO and NOS increased, the thickness of carotid intima-media became thinner and the plaque score decreased. This study provides a basis for elucidating the role of statins in the body.

Keywords: Simvastatin, pravastatin, atorvastatin, comparison of efficacy, atherosclerosis, adverse reaction.

INTRODUCTION

In recent years, the incidence and mortality of cardiovascular and cerebrovascular diseases are increasing year by year (Dindo *et al*., 2014; Brian *et al*., 2017). Atherosclerosis is the main pathological basis for inducing cardiovascular and cerebrovascular diseases. It has been proved that lipid regulating drugs can effectively control the incidence and mortality of cardiovascular and cerebrovascular diseases (Cahill *et al*., 2015). The clinical application of the amyl two acyl coenzyme A reductase inhibitor is the most widely used. It can regulate the activity of HMG-Co A reductase, reduce the synthesis of cholesterol, and decrease the secretion of liver lipoprotein to regulate blood glucose (Daniel *et al*., 2011). The use of statins can significantly reduce plasma cholesterol and LDL-C levels and significantly reduce the rate of disability and mortality of coronary and ischemic stroke, without increasing the risk of non CHD death (Dimitry *et al*., 2017). Based on the results of clinical studies, statins are widely recognized as the only lipid lowering drugs that can reduce the mortality and disability rate of patients with coronary heart disease (Feig *et al*., 2011).. In recent years, a large number of studies have suggested that statins have achieved such significant therapeutic effects on cardiovascular and cerebrovascular diseases, in addition to the effect of lipid regulating, and also benefit from a variety of non - lipid - regulating effects. Studies have shown that the non - lipid effects of statins include improving vascular endothelial function (Fangyang *et al*., 2018), inhibiting thrombus formation, anti-inflammatory, antioxidation and stabilizing atherosclerotic plaques, some of which are achieved by lowering plasma cholesterol levels, and some are not related to lowering plasma cholesterol levels. Although studies have shown that lipid modulation can explain the more benefits of statins in clinical applications, more studies support the clinical benefits of statins, which may play an important role in the prevention and treatment of atherosclerosis and coronary heart disease (Bergmann *et al*., 2016).

Simvastatin can reduce the neointima of carotid artery in normal cholesterol rabbits caused by endotheliosis, and the injection of methrovalic acid at the injured site can prevent the inhibition of fluvastatin on neointimal hyperplasia (Ghoneum *et al*., 2015). Fluvastatin can inhibit intimal thickening caused by endothelial damage when it can not reduce the dosage of serum cholesterol. Cerivastatin can through inhibiting SMC proliferation and infiltration of macrophages and inhibit the intimal thickening caused by balloon catheter (Hu, 2013). All in all, these studies suggest that statins inhibit the proliferation of SMC and have nothing to do with lipid regulation, and that the antiproliferative effect of statins may be associated with the inhibition of the synthesis of SMC in the synthesis of mevalolate (Kenichi *et al*., 2014). Statin therapy not only causes changes in lipid levels in circulation, but also changes the capacity and composition of lipid nuclei in atherosclerotic plaques. The study found that simvastatin and pravastatin can dose dependently inhibit the synthesis of cholesterol in macrophages induced by Ox-LDL (Liu *et al*., 2016). The addition of metholopulic acid or its derivatives can prevent the inhibition of statins, indicating that the non sterol derivatives of metholopyl acid participate in the cytotoxicity and esterification of Ox-LDL mediated exogenous cholesterol into macrophages. The lipid-regulating effect of statins can make plaque smaller, and

**Corresponding author:* e-mail: sdcyyylgt@163.com

increase the stability of plaque by reducing the lipid components in the plaque, changing the physiological and biochemical characteristics of the fat nucleus, or reducing the size of the macrophage foamy cells and the area of the fingerprint (Mellotte *et al*., 2015). The aim of this study is to investigate the effect and mechanism of different statins on atherosclerosis patients.

MATERIALS AND METHODS

180 cases of atherosclerotic patients admitted in 2016 were selected. Among them, there were 94 males and 81 females, aged 35~75 years, with an average age of (51.2 ±7.4) years. Inclusion criteria: (1) the patients were diagnosed as atherosclerotic patients after color Doppler ultrasound examination; (2) the patients had not taken any blood lipid regulating drugs within 15 d before receiving treatment; (3) the patients had no obvious immune rejection reaction; (4) the patients had no surgical history for half a year; 5 patients had no blood system disease. Exclusion criteria: severe liver dysfunction, renal insufficiency, and severe failure of thyroid function. 180 patients with atherosclerosis were randomly divided into 4 groups according to the number method. As the control group, simvastatin group, pravastatin group and atorvastatin group, 45 cases in each group. All patients or their families were informed of the informed consent form of the medical ethics research committee before the treatment. Research drugs: Simvastatin tablets 20 mg/ tablets, pravastatin 20 mg/ tablets, atorvastatin 20 mg/ tablets.

All patients were treated with low sugar and low fat diet during admission. The patients in the control group were treated with conventional diet control, antiplatelet drugs, anticoagulants and non statins; simvastatin group was treated with simvastatin on the basis of routine treatment. Pravastatin was given to pravastine on the basis of conventional therapy. Atorvastatin group was treated with atorvastatin on the basis of routine treatment. The dosage was 20 mg/ times and 1 times /day.

Detection index

All patients were treated with venous blood before treatment, and the levels of Triacylglycerol (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) were measured. After treatment for 6 months, the levels of TG, TC, HDL-C and LDL-C were measured again according to the same method. The 4 groups of patients were treated with color Doppler ultrasound before and after treatment. The thickness of in-tima-media thickness (IMT) was measured and the maximum diameter and thickness of the atherosclerotic plaque were measured. The content of nitric oxide NO and nitric oxide synthase (NOS) in blood was detected by spectrophotometer. NO and NOS operate according to the corresponding kit instructions. Count the number of cases of adverse reactions in patients.

Evaluation of curative effect

Referring to previous studies, if TG decreased more than 40%, TC decreased by 20% to 40%, HDL-C increased more than 0.26 mmol/L or LDL-C decreased more than 20%, it was effective for treatment, if TG decreased more than 20%, TC decreased 10%20%, HDL-C increased more than 0.10 mmol/L or LDL-C decreased more than 10%, all of which were effective if any of the above indexes were not reached. The representative is null and void.

STATISTICAL ANALYSIS

SPSS 17 statistical software was used in the data analysis. The measurement data were expressed with mean standard deviation (x±s). The variance analysis was used before and after treatment in each group. The rank sum test was used for the grade data. The difference of $P < 0.05$ was statistically significant.

RESULTS

Changes of blood lipid

We compared the levels of TG, TC, HDC-C and LDL-C after treatment in each group. The results were as follows: (1) The difference in the TG level of the simvastatin group, pravastatin group, atorvastatin calcium group and the control group was statistically significant ($F = 11.257$, $P = 0.000$). (2) There was a significant difference in the level of TC between simvastatin group, pravastatin group, atorvastatin calcium group and control group after treatment ($F = 16.139$, $P = 0.000$). (3) There was a significant difference in HDL-C level between simvastatin group, pravastatin group, atorvastatin calcium group and control group after treatment ($F = 14.756$, $P = 0.000$). (4) There was a significant difference in LDL-C level between the simvastatin group, pravastatin group, atorvastatin calcium group and the control group ($F = 28.351$, $P = 0.000$), as shown in table 1.

Comparison of the effect of lipid regulating before and after treatment

The efficiency of simvastatin group, pravastatin group and atorvastatin group was compared with the control group. The difference was statistically significant ($Z = -3.120$, -2.650 and 2.750, $P = 0.000$, 0.017 and 0.054), and the effective rate of simvastatin group, pravastatin group and atorvastatin group was higher than that in the control group, as shown in table 2.

The results of literature retrieval were searched through PubMed, Embase, Web of Science, CBM, CNKI and other Chinese and English databases. Initially, 514 articles were screened out. After 109 duplicate documents were

excluded, 405 articles were retained. In these articles, we excluded articles that did not meet the inclusion criteria according to the titles and abstracts of the reading articles, and got 62 articles that might meet the inclusion criteria. After careful reading of the full text of these 38 articles, after screening by layer by layer, 20 papers are finally included in the meta analysis and systematic evaluation.

Meta analysis results

A total of 13 cohort studies in 14 articles reported total cause mortality after the use of statins in patients with chronic obstructive pulmonary disease. 10 studies showed that statins reduced the all-cause mortality in patients with chronic obstructive pulmonary disease, and the remaining 3 studies showed no correlation between statins and all-cause mortality. The random effect model of meta analysis results show that the combined OR value was 0.65,95% confidence interval (0.65-0.78), P <0.0001, the difference was statistically significant, the risk of death in patients with chronic obstructive pulmonary disease with statins is no use of statins in patients with 0.65 times, the heterogeneity of acceptable (I-squared=37.0%, P=0.087). See fig. 1.

COPD mortality

A total of 2 cohort studies reported the COPD mortality after the use of statins in patients with chronic obstructive pulmonary disease (COPD). The random effect model of meta analysis results showed that the combined OR value was 0.43,95% confidence interval (0.20-0.80), p=0.0057, the difference was statistically significant, compared with no use of statins in patients with chronic obstructive pulmonary disease, reduce COPD related mortality using statins in patients with chronic obstructive pulmonary disease. See fig. 2 of the forest map.

Mortality of cardiovascular events

A total of 3 cohort studies reported the mortality of cardiovascular events in patients with chronic obstructive pulmonary disease (COPD) after the use of statins. The random effect model of meta analysis results showed that the combined OR value was 0.53, 95% confidence interval (0.34-0.90), p=0.288, the difference was statistically significant, compared with no use of statins in patients with chronic obstructive pulmonary disease, reduce the use of statins in patients with chronic obstructive pulmonary disease COPD cardiovascular mortality. The forest map is shown in fig. 3.

Acute exacerbation of chronic obstructive pulmonary disease

A total of 4 cohort studies have reported an acute exacerbation of the use of statins in patients with chronic obstructive pulmonary disease. The random effect model of meta analysis results showed that the combined OR value was 0.59,95% confidence interval (0.45-0.78), p<0.0001, the difference was statistically significant, compared with no use of statins in patients with chronic obstructive pulmonary disease, use of statins in patients with chronic obstructive pulmonary disease in acute exacerbation of COPD risk reduction. The forest map is shown in fig. 4.

Results of nursing intervention

The body mass index and GHQ-12 (General Health Questionnaire) scores in the experimental group were significantly better than those in the control group. The difference between the two groups was statistically significant (P<0.05), see table 1. After nursing intervention, the scores of St. George's Respiratory Questionnaire (SGRQ) in the experimental group were significantly better than those in the control group, the difference between them was statistically significant (P<0.05), see table 2.

Changes of IMT and plaque before and after treatment

The IMT and the maximum diameter and thickness of the plaque after treatment were compared between the experimental group and the control group. Results: (1) the levels of IMT in simvastatin group, pravastatin group, atorvastatin calcium group and control group were statistically significant (F =6.156, P =0.000), and IMT in simvastatin group, pravastatin group and atorvastatin group were lower than those of control group. (2) The maximum diameter of plaque in the simvastatin group, pravastatin group, atorvastatin calcium group and the control group compared with the control group was statistically significant (F =7.143, P =0.000), and the maximum plaque diameter of simvastatin group, pravastatin group and atorvastatin group was lower than that of the control group. (3) The plaque thickness of simvastatin group, pravastatin group and atorvastatin group and control group compared with the control group was statistically significant (F =11.268, P =0.000), and the plaque thickness of simvastatin group, pravastatin group and atorvastatin group was lower than that of the control group (table 3).

Comparison of the content of NO and NOS before and after treatment

We compared the contents of NO and NOS between the experimental group and the control group after repeated treatment. Results: (1) The NO content of simvastatin group, pravastatin group, atorvastatin calcium group and control group compared with the control group was statistically significant (F =15.421, P =0.000), and the simvastatin group, pravastatin group and atorvastatin group NO were lower than the control group. (2) The NOS content of simvastatin group, pravastatin group, atorvastatin calcium group and control group compared with the control group was statistically significant (F =7.618, P =0.000), and the simvastatin group, pravastatin group and atorvastatin group NOS were lower than the control group (table 4).

Table 1: Changes of blood lipid before and after treatment

Group	Stage	TG	TC	HDL-C	LDL-C
Control group	Before treatment	2.14±0.58	5.17±1.58	1.44±0.85	4.26±1.35
	After treatment	1.89±0.61	5.02±1.41	1.65±0.68	4.12±1.27
Simvastatin group	Before treatment	2.01±0.83	5.24±1.24	1.52±0.78	4.61±1.22
	After treatment	1.38±0.45	3.48±1.03	2.28±0.55	2.35±0.87
Pravastatin group	Before treatment	1.95±0.75	5.12±1.82	1.42±0.37	4.46±1.38
	After treatment	1.25±0.48	2.94±1.13	2.02±0.46	2.18±0.83
Atorvastatin group	Before treatment	2.12±0.74	5.28±1.74	1.85±0.52	4.72±1.52
	After treatment	1.52±0.46	4.08±1.54	2.61±0.41	2.45±0.76

Table 2: Evaluation of the effect of lipid regulating before and after treatment

Group	Obviously effective	Partial validity	Invalid
Control group	18(40.0%)	23(51.1%)	4(8.9%)
Simvastatin group	32(71.1%)	13(28.9%)	0(0.0%)
Pravastatin group	26(57.8%)	19(42.3%)	2(4.4%)
Atorvastatin group	31(68.9%)	11(24.5%)	3(6.7%)

Table 3: Change of IMT, diameter and thickness of plaque

Group	Stage	IMT	Plaque diameter	Plaque thickness
Control group	Before treatment	1.21±0.72	7.64±1.45	2.36±0.55
	After treatment	1.22±0.65	7.52±1.37	2.25±0.64
Simvastatin group	Before treatment	1.19±0.81	7.58±1.29	2.52±0.71
	After treatment	0.92±0.54	6.92±1.08	2.38±0.24
Pravastatin group	Before treatment	1.15±0.63	7.61±1.42	2.42±0.37
	After treatment	0.89±0.35	6.87±1.21	2.31±0.28
Atorvastatin group	Before treatment	1.20±0.71	7.75±1.50	2.27±0.56
	After treatment	0.94±0.39	6.98±1.14	2.14±0.34

Table 4: Comparison of the content of NO and NOS before and after treatment

Group	Stage	NO	NOS
Control group	Before treatment	34.63±6.54	12.34±8.25
	After treatment	51.42±7.85	21.42±9.17
Simvastatin group	Before treatment	33.28±6.81	12.69±7.29
	After treatment	37.95±7.24	16.38±8.54
Pravastatin group	Before treatment	34.25±7.63	12.47±6.42
	After treatment	38.69±8.35	15.28±7.21
Atorvastatin group	Before treatment	35.21±7.79	11.75±6.47
	After treatment	39.54±8.65	14.18±7.34

Table 5: Adverse reaction

Group	Headache	Nausea and vomiting	Muscle pain	Abdominal pain	Proteinuria	Total incidence
Control group	5	2	1	4	0	26.2%
Simvastatin group	1	3	0	2	1	15.5%
Pravastatin group	2	3	1	0	2	17.7%
Atorvastatin group	2	1	1	1	1	13.3%

Adverse reaction

All patients who received treatment were followed up for 6 months after treatment. The results showed that the adverse reactions of statins were low, indicating that statins were safe and effective in the process of using (table 5).

DISCUSSION

Atherosclerosis is a common multiple, systematic disease. The main feature is the accumulation of large amount of lipid material on the intima of the artery, which thickens the wall of the artery, thus reducing its physiological elasticity and flexibility (Ostojic *et al*., 2015). At the same time, thickening of arterial wall also indirectly reduces the volume of lumen, resulting in atheromatous lesions. Most of the causes of atherosclerosis are primary or secondary hypertension, hyperlipidemia, excessive fat diet, smoking, drinking and drinking (Paccez *et al*., 2014). But there are also some unusual causes, such as self cysteinyl. The literature reports that there are many complications of atherosclerosis, such as angina pectoris, myocardial infarction and cerebral infarction, so the diagnosis and treatment of atherosclerosis is bound to increase the death rate of the patients and cause a hidden danger to the safety of people's life (Wu *et al*.,2015). In recent years, with the increasing aging of the population, the incidence of atherosclerosis is also increasing in the elderly and becoming the most important disease population (Xuan, 2015). Therefore, the prevention and control of atherosclerosis in elderly patients has become a crucial problem. Studies have shown that in the pathological study of atherosclerosis, the degree of inflammation and plaque rupture is positively related. Therefore, the relevant scholars put forward that we should control the rupture of atherosclerotic plaques by regulating the inflammatory response, so as to regulate the cure rate of atherosclerosis.

Statins are an effective reductase inhibitor, which can reduce the content of cholesterol by inhibiting the synthesis of cholesterol in the liver, thereby reducing the concentration of cholesterol in plasma and tissue cells (Yan *et al*., 2016). In addition, statins can reduce the proliferation and growth rate of vascular smooth muscle cells by inhibiting the inflammatory response in vascular endothelial cells, promote the self regulating force of vascular cells, improve the degree of arteriosclerosis, and reduce the complication rate of thrombus. Studies have shown that the effect of statins on atherosclerosis is achieved through a variety of mechanisms, including directly acting on atherosclerotic plaques of arterial wall (Zhu *et al*., 2015). Fluvastatin and simvastatin can also inhibit acetylated LDL and inhibit cholesterol esterification and deposition in cultured macrophages. The experiments of fluvastatin, simvastatin and lovastatin showed that the drug could be independent of its lipid regulating performance and slowed down the migration and proliferation of smooth cells in a dose dependent manner. The antiproliferative efficacy of fluvastatin against the neointimal hyperplasia of normal cholesterol rabbits has proved that the effect of statins is beyond its pure lipid performance (Qin *et al*., 2015). The drug can inhibit the biosynthesis of isoprene locally and directly produce atherosclerosis in the arterial wall. Atorvastatin and simvastatin play an inhibitory role on platelet deposition to fight atherosclerosis (Tang *et al*., 2017). Statin lipid-lowering drugs have similar lipid regulating effects, but their regulation effects on atherosclerosis development and platelet response are markedly different. Statin lipid-lowering drugs regulate platelet response to vascular injury (Tomotaka *et al*., 2010). The effect of atorvastatin on platelet deposition and prevention of atherosclerotic development was observed (Tural *et al*., 2015). The results showed that atorvastatin could significantly reduce the blood platelets at the high shear rate of the blood vessel wall with mild injury and delay the development of coronary artery injury. The above findings are consistent with the clinical efficacy of the drug in the treatment of early atherosclerosis.

CONCLUSION

In this study, the effects of simvastatin, pravastatin and atorvastatin on the treatment of atherosclerotic patients were investigated. The blood lipid levels, the maximum diameter and thickness of the carotid IMT and plaque were analyzed before and after the treatment and the safety of statins was studied. It is concluded that statins are safe, effective and reliable for the treatment of atherosclerosis, and worthy of clinical promotion. The results also showed that after 6 months of taking statins, the levels of NO and NOS increased, the thickness of carotid intima-media became thinner and the plaque score decreased. This study is similar to related reports. Statins can reduce the levels of NO and NOS in atherosclerotic patients. But in this study, due to the small sample size and short research time, there is a certain degree of error in the accuracy of the results. Considering the time of action of statins and the stability of the patients in the patient's body, more time is needed. Therefore, the results of this experiment have certain guiding significance, but the accuracy still needs further large sample analysis. This study analyzed the effects of drugs on the level of blood NO and NOS in patients, and speculated the possible mechanisms of statins on the patients with atherosclerosis, providing a basis for elucidating the role of drugs in the body.

REFERENCES

Bergmann A, Thuler LC, Moore MA and Nam BH (2016). Construction of modern logistics distribution center. *Logi. Tech.*, **2**(4): 203-214.

Brian T, Weihua G, Alan T, James H and Mathew C (2017). Apolipoprotein B is associated with carotid atherosclerosis progression independent of individual cholesterol measures in a 9-year prospective study of Multi-Ethnic Study of Atherosclerosis participants. *J. Clini. Lipid.*, **11**(5): 1181-1191.

Cahill G, Tran L, Huang YC and Ou CW (2015). Thoughts on the development of modern pharmaceutical logistics. *Busin. Rese.*, **1**(1): 27-38.

Daniel Ks, Maria W and Irena L (2011). Immunization with cationized BSA inhibits progression of disease in ApoBec-1/LDL receptor deficient mice with manifest atherosclerosis. *Immun.*, **216**(6): 663-669.

Dimitry A, Veronika A, Victor V, Alexander N and Yuri V (2017). The phenomenon of atherosclerosis reversal and regression: Lessons from animal models. *Experi. Molec. Patho.*, **102**(1): 138-145.

Dindo D, Demartines N and Clavien PA (2014). Using pharmaceutical economics to guide drug pricing: Pricing and effective management of drugs with different economies. *Fore. Medic.*, **240**(2): 205-213.

Fangyang W, Lihui W, Yi L, Nannan W, Yating W and Qi C (2018). PAC-1 and its derivative WF-210 Inhibit Angiogenesis by inhibiting VEGF/VEGFR pathway. *Europ. J. Pharm.*, **821**: 29-38.

Feig J, Shang N, Rotllan Y, Vengrenyuk C and Wu R (2011). Statins promote the regression of atherosclerosis via activation of the CCR7-dependent emigration pathway in macrophages. *PLoS One*, **6**(2): 28534.

Ghoneum M, Felo N, Nwaogu OM, Fayanju IY, Jeffe JA and Margenthaler DB (2015). Logistics help pharmaceutical distribution competition. *Log. Tech. App.*, **1**(2): 73-82.

Hu J (2013). Development and application of drug supply chain management system. *Chi. Pha.*, **6**(2): 25-30.

Kenichi K, Takashi K, Hironori K, Yoshiki M, Yuichi O, Shigeho T and Yasushi O (2014). Effect of Atorvastatin Therapy on Fibrous Cap Thickness in Coronary Atherosclerotic plaque as assessed by optical Coherence Tomography: The EASY-FIT Study. *J. The Ameri. Coll. Card.*, **64**(21): 2207-2217.

Liu K, Chen XZ, Nakamura I, Ohki S and Eslick GD (2016). Application of automatic data acquisition system in medical logistics system. *Log. Tech. Appl.* **2**(2): 135-142.

Mellotte G, Maher V, Devitt PG, Shin VY and Leung CP (2015). Pharmaceutical logistics and supply chain management. *Beijing: Peking University Medical Press*, **1**(2): 101-112.

Ostojic SM, Knezevic DR, Perisic M, Jurisic V, Knezevic SM (2015). The importance of choice of resection procedures in T1 and T2 stage of carcinoma of the ampulla of Vater. *J. BUON.*, **20**(5): 1206-1214.

Paccez J, Vogelsang M and Parker M (2014). The receptor tyrosinekinase Axl in cancer: biological functions and therapeutic implica-tions. *Int. J. Cancer*, **134**(5): 1024-1033.

Qin T and Hou Y (2015). Drug supply chain information flow and its application. *Pharm. Devel.*, **2**(1): 13-16.

Tang N, Li X and Huo F (2017). Effect of levofloxacononone chalcone derivatives on the apoptosis and autophagy of human HCC SMMC-7721 cells. *West Chi. J. Phar. Sci.*, **32**(1): 28-32.

Tomotaka D, Katsumi M, Shinya O,Takayuki Y, Naotake Y and Hiroshi T(2010). Early intensive statin treatment for six months improves long-term clinical outcomes in patients with acute coronary syndrome (Extended-ESTABLISH trial): A follow-up study. *Athero*., **210**(2): 497-502.

Tural D and Kivrak Salim (2015). Is there any relation between PET-CT SUV_{max} value and prognostic factors in locally advanced breast cancer? *J. Buon.*, **20**(5): 1282-1286.

Wu H, Liang H and Sun H (2015). Neurosurgery patients nosocomial infection phase locked for element analysis. *Exp. And Bed Dis. In Mag.*, **9**(6): 14-17.

Xuan Z (2015). Study of optimal control of drug stock in hospital. *Chi. Pha.*,**1**(3): 59-66.

Yan Z, Na-Qiong W, Sha L, Cheng Z and Yuan-Lin G (2016). Non-HDL-C is a Better Predictor for the Severity of Coronary Atherosclerosis Compared with LDL-C. *Hea., Lun. Circul.*, **25**(10): 975-981.

Zhu Y and Chen W (2015). Chinese herbal medicine logistics company access standards. *Med. Wor.*, **20**(6): 1585-1591.