HOSTED BY
ELSEVIER

Contents lists available at ScienceDirect

Journal of Acute Disease

journal homepage: www.jadweb.org

Original article http://dx.doi.org/10.1016/j.joad.2016.08.023

Effects of Shuxuetong injection applied in acute ischemic stroke

Wei Zhang*

Department of Encephalopathy II, Wei Fang Traditional Chinese Hospital, Weifang 261041, Shandong, China

ARTICLE INFO

Article history:
Received 2 Aug 2016
Accepted 18 Aug 2016
Available online 20 Sep 2016

Keywords:
Ischemic stroke
Shuxuetong injection
Nerve function
Lipid metabolism
Blood coagulation function

ABSTRACT

Objective: To study the effects of Shuxuetong injection in adjuvant treatment of ischemic stroke on the degree of nerve injury, lipid metabolism and blood coagulation function.

Methods: Patients with ischemic stroke admitted in our hospital during the period from May 2012 to May 2015 were selected for retrospective analysis. They were divided into the control group receiving regular treatment and the Shuxuetong group receiving adjuvant treatment with Shuxuetong injection. One and the three months after treatment, serum was collected and nerve injury molecules, indexes of lipid metabolism and blood coagulation function were measured.

Results: One month after treatment, the contents of neuron-specific enolase, S100 calcium binding protein B, total cholesterol, triglyceride, low-density lipoprotein, oxidized low-density lipoprotein, thromboxane B_2, fibrinogen and D-dimer in the serum of patients from Shuxuetong group were significantly lower than those of control group. The contents of high-density lipoprotein and 6-keto prostaglandin $F_{1\alpha}$ were significantly higher than those of control group. Three months after treatment, the contents of neuron-specific enolase, S100 calcium binding protein B, total cholesterol, triglyceride, low-density lipoprotein, oxidized low-density lipoprotein, thromboxane B_2, fibrinogen and D-dimer in the serum of patients from Shuxuetong group were significantly lower than those of control group. The contents of high-density lipoprotein and 6-keto prostaglandin $F_{1\alpha}$ were significantly higher than those of control group.

Conclusions: Adjuvant treatment with Shuxuetong injection can reduce the injury of nerve function of patients with ischemic stroke and improve blood lipid metabolism and blood coagulation function, which is an effective drug for the treatment of ischemic stroke.

1. Introduction

Ischemic stroke is a common disease in neurology with high disability rate and mortality rate, bringing great burden to the family and society. Atherosclerosis is a pathological basis of ischemic stroke, and local thrombosis will lead to interruption of blood flow and cerebral hypoxic-ischemic damage[1,2]. Due to the poor tolerance of nerve cells to ischemia and hypoxia, cerebral infarction within a short time will cause irreversible damage. Although thrombolysis, intervention and other treatment methods are able to make the brain tissue get blood reperfusion, the patients will still have neurological dysfunction in various degrees. Besides, there is a big risk of relapse of cerebral infarction in the recovery process of neurological function for patients with ischemic stroke, which will further increase the injury of nerve function[3,4].

It is recognized that the abnormal lipid metabolism and coagulation function are closely related to the occurrence and development of atherosclerosis. Correcting lipid metabolism and abnormal blood coagulation is the key measure to treat ischemic stroke, which can not only improve the recovery of nerve function, but also reduce the risk of stroke recurrence. Lipid-lowering drugs and anticoagulant drugs commonly used in western medicine include atorvastatin, aspirin and clopidogrel, which belong to conventional drugs for the secondary prevention of ischemic stroke with the exact lipid-lowering and

*Corresponding author: Wei Zhang, Department of Encephalopathy II, Wei Fang Traditional Chinese Hospital, Weifang 261041, Shandong, China.
Tel: +86 15054571162, +86 05368060128
E-mail: zwprob@126.com

Peer review under responsibility of Hainan Medical College. The journal implements double-blind peer review practiced by specially invited international editorial board members.

anticoagulant effect[5–7]. But for patients having had ischemic stroke, the situation of lipid metabolism and abnormal coagulation function *in vivo* is more serious, and the effect is not ideal depending only on western medicine. Shuxuetong injection is a traditional Chinese medicine with the effect of promoting blood circulation to remove blood stasis and can regulate lipid metabolism and blood coagulation function. In the following study, the clinical effects of Shuxuetong injection in adjuvant treatment of ischemic stroke were analyzed.

2. Materials and methods

2.1. Research objects

Patients with ischemic stroke treated in our hospital during the period from May 2012 to May 2015 were enrolled in the research. All the patients were in line with the diagnostic criteria of cerebral infarction according to Internal Medicine (8th edition)[8] and the diagnostic criteria of stroke according to Standards of Syndrome-Differentiated Diagnosis of Stroke[9], admitted to the hospital within 72 h after onset and having complete medical records. The following cases were excluded: patients complicated with cerebral tumor and cerebral trauma, cerebral hemorrhage and heart, liver and kidney insufficiency. A total of 74 patients were enrolled in the two groups of Shuxuetong group and control group according to the different treatment regimens after the medical records were analyzed retrospectively.

2.2. Therapeutic methods

Patients of the two groups were given conventional symptomatic and supportive treatment, including the maintenance of water and electrolyte balance, nerve nutrition, improvement of encephaledema and antibiotic resistance to infection, meanwhile, given 100 mg aspirin enteric-coated tablets (*p.o.*, one time a day), 75 mg sulfate clopidogrel tablets (*p.o.*, one time a day), 20 mg atorvastatin (*p.o.*, one time a day) and 30 mg edaravone injection with 250 mL normal saline (*i.v.*, one time a day). On the basis of above regular treatments, patients of Shuxuetong group were given Shuxuetong injection treatment. The method was as follow: 8 mL Shuxuetong injection with 250 mL normal saline (*i.v.*, one time a day).

2.3. Neurologic evaluation assay

One month and three months after the treatment, the peripheral blood samples (5 mL) of the two groups were collected. After obtaining serum by centrifugation, the contents of S100 calcium binding protein B (S100B) and neuron-specific enolase (NSE) were determined by ELISA kit.

2.4. Lipid metabolism and blood coagulation indexes

One month and three months after the treatment, serum samples used in the neural damage evaluation assay were used to detect the contents of triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), oxidized low-density lipoprotein (ox-LDL), fibrinogen (FIB) and D-dimer (D–D) by using automatic biochemical analyzer and the contents of 6-keto prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$), thromboxane B_2 (TXB_2) were determined by ELISA kit.

2.5. Statistical method

The data were input and analyzed by SPSS 21.0 software. The analysis of measurement data between two groups was carried out by t test. Differences were regarded as statistically significant when $P < 0.05$.

3. Results

3.1. General data

A total of 35 patients were included in Shuxuetong group with 22 males and 13 females, age of (58.1 ± 7.2) years, body mass index (BMI) of (23.89 ± 3.24) kg/m^2. Among them, 19 cases were complicated with high blood pressure, 13 cases were complicated with diabetes and 23 cases with smoking history. A total of 39 patients were included in control group with 25 males and 14 females, age of (57.4 ± 8.3) years, BMI of (23.61 ± 3.09) kg/m^2. Among them, 22 cases were complicated with high blood pressure, 15 cases were complicated with diabetes and 24 cases with smoking history. According to the statistic analysis, there were no significant differences in sex, age, BMI and number of cases complicated with high blood pressure, diabetes and smoking history in Shuxuetong group compared with control group (Table 1).

3.2. Degree of nerve injury

One month after the treatment, the contents of serum NSE [(7.96 ± 0.93) *vs.* (11.36 ± 1.84) ng/mL] and S100B [(0.95 ± 0.11) *vs.* (1.34 ± 0.18) ng/mL] in Shuxuetong group were significantly lower than those of control group. Three months after the treatment, the contents of serum NSE [(5.47 ± 0.77) *vs.* (8.93 ± 0.94) ng/mL] and S100B [(0.64 ± 0.07) *vs.* (1.03 ± 0.14) ng/mL) in Shuxuetong group were significantly lower than those of control group. One month and three months after the treatment, National Institutes of Health Stroke Scale, Traditional Chinese Medicine syndrome score and the contents of serum NSE and S100B in the two groups were statistically significant ($P < 0.05$) (Table 2).

3.3. Blood lipid metabolic indexes

One month after the treatment, the contents of serum TC [(5.03 ± 0.67) *vs.* (5.44 ± 0.78) mmol/L], TG [(1.94 ± 0.22) *vs.* (2.38 ± 0.31) mmol/L], LDL [(2.88 ± 0.35) *vs.* (3.24 ± 0.39) mmol/L] and ox-LDL [(0.49 ± 0.07) *vs.* (0.61 ± 0.08) mg/L] in Shuxuetong group were significantly lower than those of control group. The content of HDL [(1.58 ± 0.19) *vs.* (1.39 ± 0.14)

Table 1
The clinical data of the two groups.

Parameters	Shuxuetong group (n = 35)	Control group (n = 39)
Sex (male/female)	22/13	25/14
Age (years)	58.10 ± 7.20	57.40 ± 8.30
BMI (kg/m^2)	23.89 ± 3.24	23.61 ± 3.09
High blood pressure [n (%)]	19 (54.29)	22 (56.41)
Diabetes [n (%)]	13 (37.14)	15 (38.46)
Smoking [n (%)]	23 (65.71)	24 (61.54)

Table 2
Comparison on degree of nerve injury between the two groups. ng/mL.

Parameters	Shuxuetong group (n = 35)	Control group (n = 39)
One month after treatment		
NSE	7.96 ± 0.93*	11.36 ± 1.84
S100B	0.95 ± 0.11*	1.34 ± 0.18
Three months after treatment		
NSE	5.47 ± 0.77*	8.93 ± 0.94
S100B	0.64 ± 0.07*	1.03 ± 0.14

Data are represented as mean ± SD. *: $P < 0.05$ compared with control group.

mmol/L] was significantly higher than that of control group. Three months after the treatment, the contents of serum TC [(4.65 ± 0.61) *vs.* (5.17 ± 0.72) mmol/L], TG [(1.68 ± 0.19) *vs.* (2.14 ± 0.28) mmol/L], LDL [(2.65 ± 0.29) *vs.* (3.05 ± 0.36) mmol/L] and ox-LDL [(0.42 ± 0.05) *vs.* (0.59 ± 0.07) mg/L] in Shuxuetong group were significantly lower than those of control group. The content of HDL [(1.73 ± 0.22) *vs.* (1.42 ± 0.18) mmol/L] was significantly higher than that of control group. One month and three months after the treatment, the contents of serum of TC, TG, LDL, ox-LDL and HDL were statistically significant ($P < 0.05$) (Table 3).

3.4. Coagulative function indexes

One month after the treatment, the content of serum 6-keto-$PGF_{1\alpha}$ [(37.32 ± 5.24) *vs.* (28.34 ± 3.18) μg/L] in Shuxuetong group was significantly higher than that of control group and the contents of TXB_2 [(147.69 ± 19.36) *vs.* (203.53 ± 26.48) μg/L], FIB [(3.68 ± 0.56) *vs.* (4.92 ± 0.65) g/L] and D–D [(168.64 ± 21.48) *vs.* (227.89 ± 29.14) ng/L] were significantly lower than those of control group. Three months after the treatment, the content of serum 6-keto-$PGF_{1\alpha}$ [(45.64 ± 6.37) *vs.* (32.14 ± 3.59) μg/L] in Shuxuetong group was significantly higher than that of control group and the contents of TXB_2 [(125.23 ± 18.42) *vs.* (184.53 ± 23.18) μg/L], FIB [(3.03 ± 0.49) *vs.* (4.52 ± 0.62) g/L] and D–D [(142.54 ± 17.53) *vs.* (196.52 ± 23.54) ng/L] were significantly lower than those of control group. One month and three months after the treatment, the contents of serum 6-keto-$PGF_{1\alpha}$, TXB_2, FIB and D–D were statistically significant ($P < 0.05$) (Table 4).

Table 3
Comparison on blood lipid metabolic indexes of the two groups.

Parameters	Shuxuetong group (n = 35)	Control group (n = 39)
One month after treatment		
TC (mmol/L)	5.03 ± 0.67*	5.44 ± 0.78
TG (mmol/L)	1.94 ± 0.22*	2.38 ± 0.31
LDL (mmol/L)	2.88 ± 0.35*	3.24 ± 0.39
ox-LDL (mg/L)	0.49 ± 0.07*	0.61 ± 0.08
HDL (mmol/L)	1.58 ± 0.19*	1.39 ± 0.14
Three months after treatment		
TC (mmol/L)	4.65 ± 0.61*	5.17 ± 0.72
TG (mmol/L)	1.68 ± 0.19*	2.14 ± 0.28
LDL (mmol/L)	2.65 ± 0.29*	3.05 ± 0.36
ox-LDL (mg/L)	0.42 ± 0.05*	0.59 ± 0.07
HDL (mmol/L)	1.73 ± 0.22*	1.42 ± 0.18

Data are represented as mean ± SD. *: $P < 0.05$ compared with control group.

Table 4
Comparison on coagulative function indexes of two groups.

Parameters	Shuxuetong group (n = 35)	Control group (n = 39)
One month after treatment		
6-keto-$PGF_{1\alpha}$ (μg/L)	37.32 ± 5.24*	28.34 ± 3.18
TXB_2 (μg/L)	147.69 ± 19.36*	203.53 ± 26.48
FIB (g/L)	3.68 ± 0.56*	4.92 ± 0.65
D–D (ng/L)	168.64 ± 21.48*	227.89 ± 29.14
Three months after treatment		
6-keto-$PGF_{1\alpha}$ (μg/L)	45.64 ± 6.37*	32.14 ± 3.59
TXB_2 (μg/L)	125.23 ± 18.42*	184.53 ± 23.18
FIB (g/L)	3.03 ± 0.49*	4.52 ± 0.62
D–D (ng/L)	142.54 ± 17.53*	196.52 ± 23.54

Data are represented as mean ± SD. *: $P < 0.05$ compared with control group.

4. Discussion

Aspirin and atorvastatin, respectively, are the western medicine drugs with the effects of anticoagulation and lipid-lowering, which are used in the secondary prevention treatment of ischemic cerebral infarction[10–13]. However, for patients having had ischemic cerebral infarction, it is not enough to effectively correct the abnormal blood coagulation function and lipid metabolism only by western medicine and the risk of re-infarction becomes much higher. Shuxuetong injection is made only from Chinese medicines with main components of lumbricus and leech which can promote blood circulation to remove blood stasis. Modern pharmacological studies confirmed that lumbricus and leech can improve microcirculation, reduce blood viscosity and also directly activate plasminogen and dissolve the fibrous protein[14,15]. In the process of ischemia and hypoxia injury, a variety of biomarker molecules in the endochylema of neurons and neurogliocyte will be released out of the cell, and then enter the blood circulation through the blood brain barrier. S100B protein is a kind of acidic calcium binding protein, which is highly expressed in neurons promoting axonal growth and neuronal differentiation[16,17]. NSE is a kind of enolization dimer enzyme isozyme in neurons which can regulate the cellular energy metabolism[18,19]. After the use of adjuvant therapy of Shuxuetong injection in this study, through the detection of the contents of the above two nerve damage markers to reflect the degree of injury of nerve function, the results revealed that the contents of serum S100B and NSE in Shuxuetong group were significantly lower than those of control group, which indicated that Shuxuetong injection can reduce the nerve injury in patients with ischemic cerebral infarction during rehabilitation.

Abnormal lipid metabolism is an important feature of patients with ischemic cerebral infarction, which can increase the blood viscosity and also can cause lipid deposition in endarterium and form the atheromatous plaque. TG and cholesterol are important lipid components in the body, and high levels of TG and cholesterol in the serum are also considered to be a risk factor for cerebral apoplexy. Cholesterol can be deposited in endarterium and become an important component of atheromatous plaque, and TG can accelerate the process of lipid deposition and promote the formation of atheromatous plaque[20,21]. LDL can carry cholesterol to the peripheral tissue, and get into the endarterium oxidized as ox-LDL being able to further be swallowed by macrophages, and then form foam cells[22,23]. HDL can transport cholesterol in peripheral tissues to the liver, which has an inhibitory effect on

the deposition of atherosclerotic plaque[24]. The abnormal lipid metabolism is closely related to the occurrence of ischemic cerebral infarction. And if the abnormal lipid metabolism *in vivo* could not be effectively corrected, the risk of recurrence of cerebral infarction will be increased. Lumbricus and leech in Shuxuetong injection have pharmacological effects in regulating blood lipid metabolism. Blood lipid metabolic indexes were analyzed the results showed that the contents of serum TC, TG, LDL and ox-LDL in Shuxuetong group were significantly lower than those of control group and the content of HDL was significantly higher than that of control group, which indicated that adjuvant treatment with Shuxuetong injection can improve the blood lipid metabolism in patients with ischemic cerebral infarction during rehabilitation.

In the course of ischemic cerebral infarction, the rupture of the atherosclerotic plaque can cause local thrombosis, leading to obvious abnormal blood coagulation function in the body. Thromboxane A_2 and prostaglandin $F_{1\alpha}$ are important molecules in regulating coagulation function and forming thrombus and their metabolites are TXB_2 and 6-keto-$PGF_{1\alpha}$. TXB_2 and 6-keto-$PGF_{1\alpha}$ in the body are extremely stable. Through the detection of the contents of the above two metabolites the function of thromboxane A_2 (TXA_2) and $PGF_{1\alpha}$ *in vivo* can be reflected. In the course of forming arterial thrombus, TXA_2 can increase the expression of platelet membrane diabetes IIa/IIIas receptors and promote platelet activation and aggregation. $PGF_{1\alpha}$ can antagonize the function of TXA_2, relax blood vessels and improve the blood flow perfusion[25,26]. FIB is a blood coagulation factor of hepatic synthesis, directly involves in the process of blood coagulation and can combine with platelet and aggregate the platelet through the platelet membrane diabetes compound IIb-IIIa. D–D is a frbrin monomer formed by fibrinogen and degradation product crosslinked by the activation factor X, which can reflect hyperfibrinolysis and hypercoagulable state. Coagulative function indexes were analyzed and the results showed that the contents of serum TXB_2, FIB and D–D in Shuxuetong group were significantly lower than those of control group and the content of 6-keto-$PGF_{1\alpha}$ was significantly higher than that of control group, which indicated that adjuvant treatment with Shuxuetong injection can improve the coagulation function in patients with ischemic cerebral infarction during rehabilitation.

In summary, adjuvant treatment with Shuxuetong injection can alleviate the injury of nerve function, improve the blood lipid metabolism and coagulation function in patients with ischemic cerebral infarction which is an effective drug for the treatment of ischemic cerebral infarction.

Conflict of interest statement

The author reports no conflict of interest.

References

[1] Kristoffersen DT, Helgeland J, Waage HP, Thalamus J, Clemens D, Lindman AS, et al. Survival curves to support quality improvement in hospitals with excess 30-day mortality after acute myocardial infarction, cerebral stroke and hip fracture: a before-after study. *BMJ Open* 2015; **5**(3): e006741.

[2] Li S, Sun X, Bai YM, Qin HM, Wu XM, Zhang X, et al. Infarction of the corpus callosum: a retrospective clinical investigation. *PLoS One* 2015; **10**(3): e0120409.

[3] Nolte CH, Audebert HJ. [Management of acute ischemic stroke]. *Dtsch Med Wochenschr* 2015; **140**(21): 1583-6. German.

[4] Nakashima T, Noguchi T, Haruta S, Yamamoto Y, Oshima S, Nakao K, et al. Prognostic impact of spontaneous coronary artery dissection in young female patients with acute myocardial infarction: a report from the Angina Pectoris-Myocardial Infarction Multicenter Investigators in Japan. *Int J Cardiol* 2016; **207**: 341-8.

[5] Park JY, Rha SW, Choi B, Choi JW, Ryu SK, Kim S, et al. Impact of low dose atorvastatin on development of new-onset diabetes mellitus in Asian population: three-year clinical outcomes. *Int J Cardiol* 2015; **184**: 502-6.

[6] Hsu JC, Maddox TM, Kennedy K, Katz DF, Marzec LN, Lubitz SA, et al. Aspirin instead of oral anticoagulant prescription in atrial fibrillation patients at risk for stroke. *J Am Coll Cardiol* 2016; **67**(25): 2913-23.

[7] Shiue HJ, Sands KA. Extended use of clopidogrel and aspirin after ischemic stroke. *Am J Health Syst Pharm* 2016; **73**(10): 611.

[8] Ge JB, Xu YJ. [*Internal medicine*]. 8th ed. Beijing: People's Medical Publishing House; 2013, p. 473-4. Chinese.

[9] Encephalopathy Emergency Cooperative Group of State Administration of Traditional Chinese Medicine. [Standards of syndrome-differentiated diagnosis of stroke (trial)]. *J Beijing Univ Tradit Chin Med* 1994; **17**(3): 64-6. Chinese.

[10] Song T, Liu J, Tao X, Deng JG. Protection effect of atorvastatin in cerebral ischemia-reperfusion injury rats by blocking the mitochondrial permeability transition pore. *Genet Mol Res* 2014; **13**(4): 10632-42.

[11] Tuttolomondo A, Di Raimondo D, Pecoraro R, Maida C, Arnao V, Della Corte V, et al. Early high-dosage atorvastatin treatment improved serum immune-inflammatory markers and functional outcome in acute ischemic strokes classified as large artery atherosclerotic stroke: a randomized trial. *Medicine (Baltimore)* 2016; **95**(13): e3186.

[12] Uchiyama S, Ishizuka N, Shimada K, Teramoto T, Yamazaki T, Oikawa S, et al. Aspirin for stroke prevention in elderly patients with vascular risk factors: Japanese Primary Prevention Project. *Stroke* 2016; **47**(6): 1605-11.

[13] Li Z, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Treatment effect of clopidogrel plus aspirin within 12 hours of acute minor stroke or transient ischemic attack. *J Am Heart Assoc* 2016; **5**(3): e003038.

[14] Müller C, Mescke K, Liebig S, Mahfoud H, Lemke S, Hildebrandt JP. More than just one: multiplicity of hirudins and hirudin-like factors in the medicinal leech, hirudo medicinalis. *Mol Genet Genomics* 2016; **291**(1): 227-40.

[15] Amorim AM, de Oliveira UC, Faria F, Pasqualoto KF, Junqueira-de-Azevedo Ide L, Chudzinski-Tavassi AM. Transcripts involved in hemostasis: exploring salivary complexes from *Haementeria vizottoi* leeches through transcriptomics, phylogenetic studies and structural features. *Toxicon* 2015; **106**: 20-9.

[16] Lai PM, Du R. Association between S100B levels and long-term outcome after aneurysmal subarachnoid hemorrhage: systematic review and pooled analysis. *PLoS One* 2016; **11**(3): e0151853.

[17] Ye H, Wang L, Yang XK, Fan LP, Wang YG, Guo L. Serum S100B levels may be associated with cerebral infarction: a meta-analysis. *J Neurol Sci* 2015; **348**(1–2): 81-8.

[18] Goksuluk H, Gulec S, Ozcan OU, Gerede M, Vurgun VK, Ozyuncu N, et al. Usefulness of neuron-specific enolase to detect silent neuronal ischemia after percutaneous coronary intervention. *Am J Cardiol* 2016; **117**(12): 1917-20.

[19] Li K, Jia J, Wang Z, Zhang S. Elevated serum levels of NSE and S-100β correlate with increased risk of acute cerebral infarction in Asian populations. *Med Sci Monit* 2015; **21**: 1879-88.

[20] Cao XL, Du J, Zhang Y, Yan JT, Hu XM. Hyperlipidemia exacerbates cerebral injury through oxidative stress, inflammation and neuronal apoptosis in MCAO/reperfusion rats. *Exp Brain Res* 2015; **233**(10): 2753-65.

[21] Nakagami T, Nishimura R, Sone H, Tajima N. The combination of elevated triglycerides and abnormal fasting glucose increases risk of cerebral infarction in patients with mild to moderate

hypercholesterolemia: a post hoc analysis of the MEGA study. *J Cardiovasc Pharmacol Ther* 2015; **20**(2): 169-73.

[22] Yang N, Lin M, Wang BG, Zeng WY, He YF, Peng HY, et al. Low level of low-density lipoprotein cholesterol is related with increased hemorrhagic transformation after acute ischemic cerebral infarction. *Eur Rev Med Pharmacol Sci* 2016; **20**(4): 673-8.

[23] Song TJ, Cho HJ, Chang Y, Youn M, Shin MJ, Jo I, et al. Low-density-lipoprotein particle size predicts a poor outcome in patients with atherothrombotic stroke. *J Clin Neurol* 2015; **11**(1): 80-6.

[24] Meng GL, Tan Y, Fang M, Yang HY, Liu XY, Zhao YX. Paradoxical elevation of high density lipoprotein cholesterol in association with lacunar-type cerebral infarction. *Med Sci Monit* 2015; **21**: 1872-8.

[25] Shao J, Fu Y, Yang W, Yan J, Zhao J, Chen S, et al. Thromboxane A_2 receptor polymorphism in association with cerebral infarction and its regulation on platelet function. *Curr Neurovasc Res* 2015; **12**(1): 15-24.

[26] Yang W, Yan A, Zhang T, Shao J, Liu T, Yang X, et al. Thromboxane A_2 receptor stimulation enhances microglial interleukin-1β and no biosynthesis mediated by the activation of ERK pathway. *Front Aging Neurosci* 2016; **8**: 8.