Tropical Journal of Pharmaceutical Research October 2023; 22 (10): 2177-2183
**ISSN:** 1596-5996 (print); 1596-9827 (electronic)


Available online at http://www.tjpr.org
**http://dx.doi.org/10.4314/tjpr.v22i10.20**

**Original Research Article**

# Safety and efficacy of salvianolate injection in preventing deep vein thrombosis after total hip replacement

**Xiaoning Liu, Yang Ju, Xiaoyong Yin*, Hui Yang, Shoujiang Han, Deming Kong, Hongbo Zhao**

*Department of Trauma, Fengfeng General Hospital of North China Medical and Health Group, Handan City, Hebei Province 056002, China*

**For correspondence:* ***Email:*** *yxy46176@outlook.com*

*Sent for review: 21 April 2023* *Revised accepted: 7 October 2023*

## *Abstract*

***Purpose:*** *To investigate the safety and efficacy of salvianolate injection in preventing deep vein thrombosis (DVT) following total hip replacement.*

***Methods:*** *A total of 114 patients who underwent total hip replacement at Department of Trauma, Fengfeng General Hospital of North China Medical and Health Group, Handan City, China from March 2019 to March 2022 were enrolled. Patients were randomly divided into study group (n = 57) and control group (n = 57). The control group received conventional treatment (low molecular weight heparin) while the study group was administered salvianolate injection combined with conventional treatment. Incidence of deep vein thrombosis (DVT) at 7 and 14 days after surgery, platelet function indices, including platelet count, glycoprotein Ⅱb/Ⅲa (GP Ⅱb/Ⅲa), and CD62P, coagulation function indices (prothrombin time (PT), fibrinogen (FIB) and D-dimer), and hemodynamics indices, viz, peak blood flow velocity (Vp) and average velocity (Va) were investigated and compared.*

***Results:*** *Incidence of DVT was 1.75 % (1/57) at 7 days and 5.26 % (3/57) at 14 days in the study group, and 5.26 % (3/57) at 7 days and 17.54 % (10/57) at 14 days in control group. Incidence of DVT in the study group was significantly reduced compared to control group 14 days after surgery ($p < 0.05$). Also, the study group had significantly lower visual analog scale (VAS) scores at 7 days and 1 month after surgery compared to control group ($p < 0.05$). Platelet count, GP Ⅱb/Ⅲa, and CD62P in the study group were significantly lower than in control group ($p < 0.05$).*

***Conclusion:*** *Salvianolate injection significantly prevents DVT after total hip replacement, improves hemodynamics, and coagulation function, and thus contributes to recovery of hip function. Further clinical trials are, however, required to validate these findings.*

***Keywords:*** *Salvianolate for injection, Total hip replacement, Lower extremity deep vein thrombosis, Coagulation function, Platelet function, Hemodynamics*



**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

Deep venous thrombosis (DVT) is caused by pathological accumulation of blood clots (thrombi) in deep veins, typically in legs. These clots can obstruct normal blood flow in affected vein, causing some clinical symptoms such as swelling, pain, and potentially severe complications. Patients with pulmonary embolism

have the highest fatality rate [1]. Hip surgery affects blood flow to limbs, and DVT easily occurs due to impaired blood circulation [2]. Some studies have pointed out that DVT after total hip replacement does not facilitate postoperative recovery of hip function in patients [3]. Low molecular weight heparin is currently the primary drug for thrombosis treatment, and it downregulates DVT incidence. However, many surgical patients still have a high incidence of thrombotic disease even after receiving treatment with low molecular weight heparin, suggesting that relevant drugs may be given for treatment on this basis [4].

*Salvia miltiorrhiza*, a traditional Chinese medical herb, is known for improving circulation of blood and alleviating blood stasis. Salvianolate is a bioactive compound extracted from *Salvia miltiorrhiza* and exhibits high clinical efficacy in improving hematological abnormalities [5,6]. Therefore, this study aimed to investigate safety and efficacy of salvianolate injection in preventing lower limb DVT after total hip replacement.

## METHODS

### Patient information

A total of 114 patients who underwent total hip replacement at Department of Trauma, Fengfeng General Hospital of North China Medical and Health Group, Handan City, China March 2019 to March 2022 were enrolled. The patients were randomly divided into study group (n = 57) and control group (n = 57). This study was approved by Ethics Committee of Fengfeng General Hospital of North China Medical and Health Group (approval no. 20181220F) and written informed consent was obtained from participants. All processes were conducted in compliance with ethical standards of the Institutional Review Board and the guidelines of Declaration of Helsinki [7], and its subsequent amendments or analogous ethical standards.

#### *Inclusion criteria*

Patients undergoing total hip replacement surgery, with normal coagulation function before surgery, without evidence of DVT after examination with Doppler ultrasound, and who have complete clinical information were included in the study.

#### *Exclusion criteria*

Patients with severe cardiac, liver, and renal dysfunction; active bleeding or bleeding tendency; acute and chronic infectious diseases; allergic constitution, severe cognitive dysfunction, coagulation dysfunction before surgery, old fracture, and previous history of hip surgery were excluded from the study.

### Procedures and management

Both groups underwent total hip replacement. In control group, patients were given targeted intervention in perioperative period based on recommendations outlined in guidelines for preventing venous thromboembolism in major orthopedic surgery in China. After surgery, heparin sodium injection (Qianhong Bio-pharma, Hangzhou, China; batch number: H32022088) was administered as an adjunct to standard treatment (5000 U subcutaneous injection for first treatment and 5000 U/12 h subcutaneous injections for a total of 14 days). After surgery, patients were instructed to perform ankle flexion and extension exercises, family members were instructed to massage lower limbs and elevate the affected limbs, and plantar vein pump was actively given for physical intervention.

Study group was additionally given salvianolate injection (GreenValley, Shanghai, China; batch number: Z20050248). Salvianolate injection (200 mg) was added to 250 mL normal saline and administered as intravenous drip, once daily for 14 days.

### Evaluation of therapeutic efficacy

#### *Incidence of DVT*

Incidence of DVT was compared at 7 and 14 - days post-surgery. Diagnostic criteria for DVT are as follows: acute onset, swelling, skin temperature rise, pain, positive Homans sign, and color Doppler ultrasonography showing no color blood flow signal in venous blood vessels.

#### *Pain degree*

Visual analog scale (VAS) evaluated pain degree [8], with scores ranging from 0 to 10. Higher scores indicate greater pain.

#### *Platelet function indices*

A 3 mL sample of fasting venous blood was obtained a day prior to surgery and 14 days after surgery. Serum was obtained through centrifugation. Levels of glycoprotein Ⅱb/Ⅲa (GPⅡb/Ⅲa) and CD62P in serum were measured using Beckman Coulter Navios flow cytometry. Platelet count was determined using

ethylene diamine tetra-acetic acid (EDTA) method.

### *Coagulation function indices*

Fasting venous blood (3 mL) was collected a day before surgery and 14 days after surgery. Serum was obtained through centrifugal. Level of prothrombin time (PT) was determined using Quaker phase I method, fibrinogen level was determined by test single diffusion method, and D-dimer level was determined by monoclonal antibody method.

### *Lower limb hemodynamics*

Mindray DC-8 color Doppler ultrasonography device was used to determine femoral vein peak velocity (Vp) and average velocity (Va) before and 14 days after surgery.

### *Hip function*

Harris score was used to analyze hip function before surgery and 3 months after surgery [9], including pain, function, deformity and motion. Score rating from 0 to 100, with a higher score indicating better hip function.

### Statistical analysis

Data were analyzed using Statistical Packages for Social Sciences software (version 22.0). Enumeration data are presented as percentages and analyzed using Chi-square test. Measurement data are expressed as mean ± standard deviation (SD) and comparisons were done using t-test. $P < 0.05$ was considered statistically significant

## RESULTS

### Incidence of DVT

Incidence of DVT was 1.75 % (1/57) 7 days after surgery and 5.26 % (3/57) 14 days after surgery in study group, and 5.26 % (3/57) and 17.54 % (10/57) in control group respectively.

### Postoperative VAS scores

Compared to control group, additional salvianolate treatment (study group) significantly reduced VAS scores 7 days and 1 month before surgery in patients (Figure 1).

### Platelet function indices

Platelet count (Figure 2 A), GPⅡb/Ⅲa (Figure 2 B), and CD62P (Figure 2 C) were significantly lower in study group compared to control group ($p < 0.05$).

### Coagulation function indices

Compared to control group, study group had significantly greater efficacy in reducing levels of fibrinogen (Figure 2 A), and D-dimer (Figure 2 B), and also, shortening prothrombin time (Figure 3 C).

### Lower limb hemodynamics

Salvianolate treatment combined with conventional treatment (study group) significantly increased Vp (Figure 4 A) and Va values (Figure 4 B) after treatment.

**Table 1:** Clinical characteristics of patients (n=57)

| Parameter | Study group | Control group | $\chi^2$/*t*-value | *P*-value |
|---|---|---|---|---|
| Gender (cases) | | | 0.316 | 0.574 |
| Male | 31 | 28 | | |
| Female | 26 | 29 | | |
| Age (years) | 63.35±5.86 | 64.07±4.93 | 0.71 | 0.479 |
| BMI (kg/m$^2$) | 22.71±2.13 | 22.95±2.46 | 0.557 | 0.579 |
| Diastolic pressure (mmHg) | 74.96±6.14 | 75.04±6.52 | 0.067 | 0.946 |
| Systolic pressure (mmHg) | 124.53±9.58 | 126.92±10.86 | 1.246 | 0.215 |
| Heart rate (times/min) | 80.47±5.03 | 81.15±4.72 | 0.744 | 0.458 |
| Primary diseases (cases) | | | 0.323 | 0.851 |
| Femoral neck fracture | 13 | 12 | | |
| Femoral head necrosis | 27 | 30 | | |
| Intertrochanteric fracture | 17 | 15 | | |
| Combined diabetes mellitus (cases) | 8 | 10 | 0.264 | 0.607 |
| Combined cardiovascular disease (cases) | 14 | 11 | 0.461 | 0.497 |

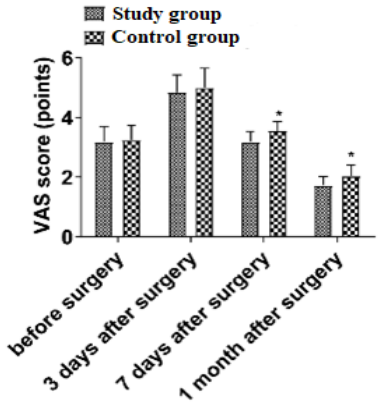


**Figure 1:** VAS scores Comparison *$P < 0.05$

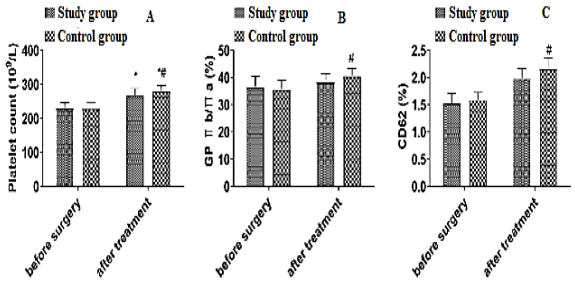


**Figure 2:** Comparison of platelet function indices. (A) Platelet count, (B) GPⅡb/Ⅲa, (C) CD62P, when compared before surgery, *$p < 0.05$; when compared to post-treatment study group, #$P < 0.05$

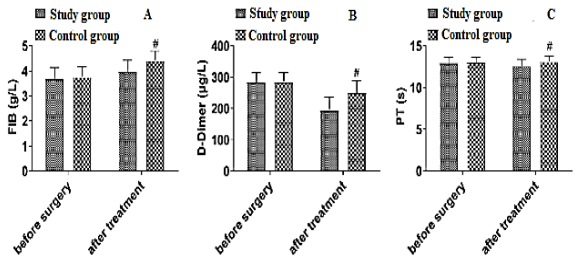


**Figure 3:** Comparison of coagulation function indices. (A) levels of fibrinogen (B) D-dimer (C) prothrombin time. #$P < 0.05$ after-treatment study compared to control group

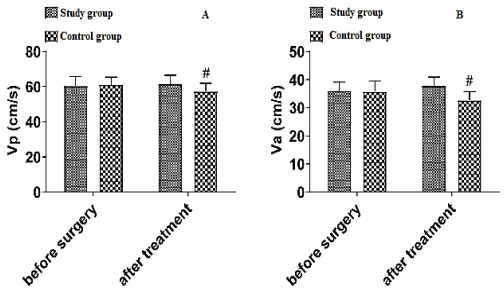


**Figure 4:** Comparison of lower limb hemodynamics (cm/s). (A) Vp and (B) Va values after treatment (#$P < 0.05$)

## Lower limb function

Pain scores (Figure 5 A), function (Figure 5 B), deformity (Figure 5 C), motion (Figure 5 D), and total scores (Figure 5 E) were significantly higher in study group compared to control group after treatment.

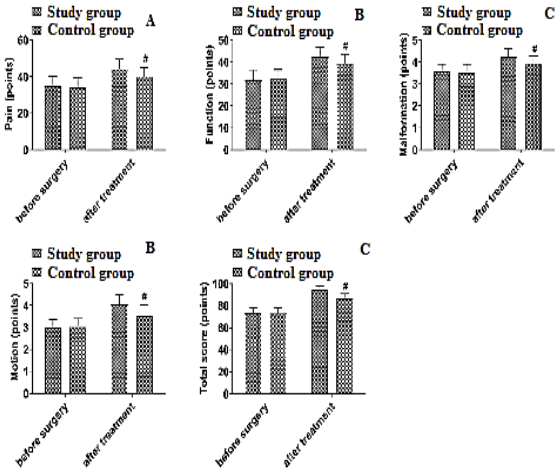


**Figure 5:** Comparison of Harris scores. (A) Pain scores, (B) Function, (C) Deformity, (D) Motion, and (E), Total scores. #$p < 0.05$ vs. control

## Incidence of adverse reactions

No noticeable side effects occurred in all patients during treatment.

# DISCUSSION

Lower limb DVT is a common clinical disease in vascular surgery. Its high incidence is in patients requiring prolonged bed rest due to surgical operations, chronic diseases, and limb movement restriction, which often results in symptoms such as pain swelling, and further induces pulmonary embolism, disability, and even death [10]. During hip replacement, veins may be damaged, and intraoperative vein blood may become hypercoagulable or stagnant, potentially increasing risk of venous thrombosis. Heparin is the main drug used in postoperative anticoagulant therapy, but it still has limitations in elderly due to large doses and clearance primarily through the kidneys. It is believed that traditional Chinese medicine has therapeutic effects on postoperative DVT [11].

*Salvia miltiorrhiza* is a traditional Chinese medical herb for stimulating circulation of blood and removing blood stasis. Pharmacological studies have demonstrated that pharmacological components of *Salvia miltiorrhiza* inhibit platelet aggregation, and thrombosis, and promote microcirculation [12]. Other studies on animal

experiments have found that *Salvia miltiorrhiza* significantly reduced whole blood viscosity and inhibited platelet aggregation under conditions of low shear rate [13]. Tanshinone in *Salvia miltiorrhiza* prevented cytokine-induced activation of endothelial cells, reducing incidence of thrombus [14].

This study revealed that salvianolate reduced incidence of DVT 14 days after surgery, suggesting that salvianolate for injection effectively prevents formation of DVT after total hip replacement. This is consistent with other studies [15], mainly because salvianolate has a positive effect on a variety of haemo-rheological indices. Additionally, it efficiently interrupts detrimental cycles involving compromised coagulation function, inhibiting capillary regeneration, and coagulation response, thereby effectively thwarting development of DVT and enhancing postoperative recuperation.

In normal human body, coagulation and fibrinolytic function are in a relatively dynamic equilibrium state. Stress reactions such as surgical trauma, mental stress, and intraoperative cold stimulation disrupt the balance of blood coagulation and anticoagulation systems, resulting in hypercoagulability and even lower limb DVT [16]. When lower extremity is severely injured, blood vessels around the injured site are damaged, tissue edema and small thrombus are formed, the microvascular system is damaged, and multiple organ failure is induced in severe cases. Fibrinogen and D-dimer serve as molecular indicators of alterations in activity of coagulation and fibrinolytic systems during formation of blood clots and pre-thrombotic state. They mirror modifications in coagulation and fibrinolytic processes within the body and act as indicators of either thrombus formation or dissolution. D-dimer is a marker of hypercoagulability and secondary hyperfibrinolysis [17]. *Salvia miltiorrhiza* acts on third stage of blood coagulation, that is, inhibits conversion of fibrinogen into fibrin, and this influences coagulation function of patients [18].

Salvianolate injection is a polyphenate compound extracted from *Salvia miltiorrhiza* with magnesium lithospermate B as main component. Pharmacological properties include enhancing blood circulation, regulating collateral vessels, alleviating blood stasis, and enhancing blood microcirculation through various mechanisms. This research demonstrated that salvianolate lowered D-dimer and fibrinogen (FIB) levels and shortened prothrombin time (PT), indicating that salvianolate significantly enhances coagulation function in patients. This is primarily attributed to impact of salvianolate on blood viscosity, platelet count, fibrinogen levels, and other hemodynamic parameters, which collectively contribute to effective improvement of patients' coagulation function. Abnormal platelet function is also an important factor leading to DVT in a hypercoagulable state. Incidence of DVT was effectively reduced by improving platelet function in patients [19]. This study found that salvianolate reduced platelet count and lowered GPⅡb/Ⅲa and CD62P levels, indicating that salvianolate effectively improves platelet function. This study also revealed that salvianolate elevated Vp and Va values, indicating that salvianolate improves lower limb hemodynamics and this is, primarily attributed to its positive impact on platelet and coagulation function.

Deep vein thrombosis (DVT) directly affects hip function of patients [20]. This study revealed that salvianolate effectively improved coagulation function of patients and reduced incidence of DVT. This suggests that salvianolate promotes recovery of hip joint function after surgery. Salvianolate is an active ingredient of *Salvia miltiorrhiza* derivates, which is water soluble and effectively improves coagulation function [21].

This research revealed that salvianolate led to an improvement in pain, function, deformity, mobility, and Harris scores. Simultaneously, it resulted in a reduction in VAS scores at both 7 days and 1 month after surgery. These findings suggest that salvianolate alleviates postoperative pain and enhances hip joint function, which may be linked to enhanced coagulation function and reduction in DVT occurrence In addition, results showed that no significant side effects occurred in all patients during treatment, suggesting that salvianolate injection has a high safety in preventing DVT formation after total hip replacement.

**Limitations of the study**

This was a single-center study with a relatively small sample size. Consequently, larger-scale stochastic clinical study is necessary to verify the reliability of these findings.

## CONCLUSION

Salvianolate injection is effective in preventing DVT after total hip replacement, improves hemodynamics and coagulation function, and contributes to postoperative hip function recovery. Nonetheless, there is a need to validate these findings in further clinical trials.

## DECLARATIONS


### *Acknowledgements*

None provided.

### *Funding*

None provided.


### *Ethical approval*

This study was approved by Ethics Committee of Fengfeng General Hospital of North China Medical and Health Group (approval no. 20181220F).

### *Availability of data and materials*

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

### *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. Xiaoning Liu and Hongbo Zhao conceived and designed the study, and drafted the manuscript. Yang Ju, Xiaoyong Yin and Hui Yang collected, analyzed and interpreted the experimental data. Shoujiang Han and Deming Kong revised the manuscript for important intellectual content. All authors read and approved the final manuscript.



## REFERENCES


1. *Zervos TM, Bazydlo M, Tundo K, Macki M, Rock J. Risk Factors associated with symptomatic deep vein thrombosis following elective spine surgery: A Case-Control Study. World Neurosurg 2020; 144(11): e460-e465.*
2. *Stewart A, Schaffer KJ, Origenes R, Shields M. Deep Vein thrombosis screening with risk assessment profile and trauma patients: a quality evaluation. J Am Coll Surg 2021; 233(5): e215-e215.*
3. *Ali Hasan M, Azeez Alsaadi M, Tahseen Mehsen J. Effectiveness of apixaban versus enoxaparin in preventing wound complications and deep venous thrombosis following total knee replacement surgery: a retrospective study. Int J Clin Pract 2021; 75(10): e14552.*
4. *Yuan Q, Wang JX, Li RL, Jia ZZ, Wang SX, Guo H, Chai LJ, Hu LM. Effects of salvianolate lyophilized injection combined with Xueshuantong injection in regulation of BBB function in a co-culture model of endothelial cells and pericytes. Brain Res 2020; 1751(1): 147185.*
5. *Behrendt CA, Twerenbold R, Blankenberg S. The everlasting challenge to identify deep vein thrombosis in both clinical practice and research. Eur Heart J 2022; 43(19): 1882-1883.*
6. *Kumamaru KK, Kumamaru H, Yasunaga H, Matsui H, Omiya T, Hori M, Suzuki M, Wada A, Kamagata K, Takamura T, et al. Large hospital variation in the utilization of Post-procedural CT to detect pulmonary embolism/Deep vein thrombosis in patients undergoing total knee or hip replacement surgery: Japanese nationwide diagnosis procedure combination database study. Br J Radiol 2019; 92(1097): 20180825.*
7. *World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.*
8. *Min L. The Efficacy and Safety of Rivaroxaban in Preventing Deep Vein Thrombosis after Hip Replacement. Indian J Pharm Sci 2020; 82(s6): 1-9.*
9. *Intiyanaravut T, Thongpulsawasdi N, Sinthuvanich N, Songtaweesap S. Efficacy and safety of dabigatran for venous thrombosis prophylaxis after knee replacement surgery in Thai patients: a prospective non-randomized controlled trial. Asian Biomed 2020; 13(6): 217-223.*
10. *Hadžimehmedagić A, Rovčanin B, Vranić H, Djedović M, Štraus S, Selimović T. Preoperative femoral vein velocity in maximal flexion is a predictor of deep vein thrombosis in patients undergoing total hip arthroplasty. Acta Clin Croat 2020; 59(3): 416-423.*
11. *Li R, Yuan M, Cheng J, Yu S, Wei W, Fu W, Prandoni P, Chen Y. Risk of post-thrombotic syndrome after deep vein thrombosis treated with rivaroxaban versus vitamin-K antagonists: A systematic review and meta-analysis. Thromb Res 2020; 196(e3): 340-348.*
12. *Ma X, Liu X, Wang G, Xia X, Yi X. The clinical efficacy of maizhiling combined with low molecular weight heparin in the treatment of deep vein thrombosis after spinal cord injury. Indian J Pharm Sci 2021; 83(6): 124-129.*
13. *Cerbasi S, Bernasconi A, Balato G, Dimitri F, Zingaretti O, Orabona G, Pascarella R, Mariconda M. Assessment*

*of deep vein thrombosis using routine pre- and postoperative duplex Doppler ultrasound in patients with pelvic trauma A prospective study. Bone Joint J 2022; 104-B(2): 283-289.*

14. *Cao W, Yang Q, Zhang W, Xu Y, Wang S, Wu Y, Zhao Y, Guo Z, Li R, Gao R. Drug-drug interactions between salvianolate injection and aspirin based on their metabolic enzymes. Biomed Pharmacother 2021; 135(3): 111203.*
15. *Lin FF, Chen B, Lin CH, Zheng K. Foot pump versus low-molecular-weight heparin for preventing deep vein thrombosis following surgery for hip and knee replacement. Int Surg 2021; 105(1/3): 389-396.*
16. *Hou J, Wang W, Cai H, Chen J, Chen B, Shen Z, Tang Y, Li J, Liu S, Mei Y, et al. Patients with right lower extremity deep vein thrombosis have a higher risk of symptomatic pulmonary embolism: A retrospective study of 1585 patients. Ann Vasc Surg 2022; 81(4): 240-248.*
17. *Pham A, Heib A, Goodman E, Cotto R, Denesopolis J, Lipsitz E. Management of distal deep vein thrombosis with warfarin versus direct oral anticoagulant agents. J vasc surg 2021; 74(4): E347-E347.*
18. *Yuan Q, Wang FJ, Jia ZZ, Zhang T, Sun J, Du XY, Wang SX, Chai LJ, Hu LM. Xueshuantong injection combined with salvianolate lyophilized injection improves the synaptic plasticity against focal cerebral ischemia/reperfusion injury in rats through PI3K/AKT/mTOR and RhoA/ROCK pathways. Brain Res 2022; 1787(7): 147923.*
19. *Howard TA, Judd CS, Snowden GT, Lambert RJ, Clement ND. Incidence and risk factors associated with venous thromboembolism following primary total hip arthroplasty in low-risk patients when using aspirin for prophylaxis. Hip Int 2022; 32(5): 562-567.*
20. *Luan P, Xu J, Ding X, Cui Q, Jiang L, Xu Y, Zhu Y, Li R, Lin G, Tian P, et al. Neuroprotective effect of salvianolate on cerebral ischemia-reperfusion injury in rats by inhibiting the Caspase-3 signal pathway. Eur J Pharmacol 2020; 872(4): 172944.*
21. *Sun D, Cui S, Ma H, Zhu P, Li N, Zhang X, Zhang L, Xuan L, Li J. Salvianolate ameliorates renal tubular injury through the Keap1/Nrf2/ARE pathway in mouse kidney ischemia-reperfusion injury. J Ethnopharmacol 2022; 293(7): 115331.*