



# Efficacy and safety of Mailuo Shutong granule combined with low molecular weight heparin in the prevention of postoperative deep venous thrombosis: a systematic review and Meta-analysis

Tianyuan Wang<sup>1,2^</sup>, Jin Song<sup>1,2</sup>, Jing Hu<sup>1,2^</sup>, Shuo Feng<sup>1,2^</sup>, Huina Zhang<sup>1,2</sup>, Hong Wang<sup>1,2</sup>, Bo Li<sup>1,2^</sup>

<sup>1</sup>Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, China; <sup>2</sup>Beijing Institute of Traditional Chinese Medicine, Beijing, China

*Contributions:* (I) Conception and design: T Wang, B Li; (II) Administrative support: None; (III) Provision of study materials or patients: T Wang; (IV) Collection and assembly of data: T Wang, J Song, B Li, H Wang, H Zhang; (V) Data analysis and interpretation: S Feng, J Hu, B Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Bo Li. Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, No. 23 Art Gallery Back Street, Dongcheng District, Beijing 100010, China. Email: libo@bjzhongyi.com.

**Background:** to systematically evaluate the efficacy and safety of Mailuo Shutong granule combined with low molecular weight heparin in the prevention of postoperative deep venous thrombosis (DVT).

**Methods:** PubMed, EMBase, Cochrane Library, China knowledge Network (CNKI), Wanfang Medical Database, Chinese Biomedical Literature Database (SinoMed) and VIP Database were searched by computer from the establishment of the database to July 3, 2020. Search and collect randomized controlled trials of Mailuo Shutong granule combined with low molecular weight heparin in the prevention of postoperative DVT. Cochrane risk bias assessment tool was used to evaluate the quality of the included study, and RevMan5.3 software was used for meta-analysis.

**Results:** A total of 61 articles about prevention of DVT after operation with Mailuo Shutong granule combined with low molecular weight heparin were searched and finally included in 4 RCT trials. A total of 465 patients were enrolled in the study. The results of Meta-analysis showed that the incidence of 1DVT: the incidence of postoperative DVT decreased by Mailuo Shutong granule combined with low molecular weight heparin in the test group and low molecular weight heparin in the control group was not statistically significant, but there was a trend of change (RR =0.47). Incidence of adverse reactions: there was no significant difference in the incidence of adverse reactions between Mailuo Shutong granule combined with low molecular weight heparin in the test group and low molecular weight heparin in the control group, but there was a change trend (RR =0.63, 95% CI: 0.26–1.50, P>0.05). Total clinical effective rate: in the included study, Zhang M reported that the total clinical effective rate of Mailuo Shutong granule combined with low molecular weight heparin in the experimental group to prevent postoperative DVT was 47%. The total clinical effective rate of low molecular weight heparin in the control group was 35%, which was statistically significant.

**Conclusions:** the clinical effect of Mailuo Shutong granule combined with low molecular weight heparin in the prevention of postoperative DVT may be better than that of low molecular weight heparin in the prevention of postoperative DVT, and may have a tendency to reduce the incidence of postoperative DVT. and does not increase the risk of anticoagulant bleeding, has good efficacy and safety. The number of existing clinical studies is small, and the quality is generally low. In order to further verify the above conclusions, more high-quality clinical RCT trials need to be carried out, and internationally recognized indicators

<sup>^</sup> ORCID: Tianyuan Wang, 0000-0002-5320-7596; Jing Hu, 0000-0001-7080-0212; Shuo Feng, 0000-0002-9155-4652; Bo Li, 0000-0002-7121-7958.

should be selected for outcome indicators.

**Keywords:** Mailuo Shutong Granules; deep venous thrombosis (DVT); meta-analysis; systematic review

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## Introduction

Deep venous thrombosis (DVT) is a venous reflux disorder caused by abnormal coagulation of blood in the deep vein. It is the third largest vascular disease besides cardio-cerebrovascular diseases, which often occurs in the blood vessels of the lower extremities (1).

Complications of pulmonary thromboembolism (PTE) in acute stage of DVT, is the main cause of amputation or death in patients with DVT. The development of PTS in chronic phase may lead to the decline of quality of life in patients with DVT, and its quality of life assessment is worse than that of other chronic diseases such as diabetes, osteoarthritis, chronic lung disease and other related diseases (2). DVT and PTE are collectively referred to as venous thromboembolic disease (VTE) (3).

Surgery is a high risk factor for the occurrence of DVT, some operations require intestinal preparation, preoperative fasting water and gastrointestinal decompression reduce blood volume and increase blood viscosity; intraoperative infusion of a large amount of hypertonic hypothermic fluid is easy to damage vascular intima, operation will damage vascular wall and tissue, activate blood coagulation system; anesthesia, cardiopulmonary bypass, long-term bed rest after operation lead to slow venous blood flow (4). According to literature (5), the incidence of lower limb DVT in unprevented hospitalized patients is as high as 10–40%, and the fatality rate within 1 month after diagnosis of DVT is about 6% (6). Correct understanding of the occurrence of DVT and reasonable prevention in the early stage are of great significance to reduce the occurrence of DVT and PTS and improve the quality of life of patients.

The existing routine methods for the prevention of postoperative DVT are physical prophylaxis and drug prophylaxis, physical prophylaxis includes early activity and mechanical prophylaxis, including intermittent inflatable pressurization device, plantar vein pump, step-by-step pressurized elastic socks and CPM machine, etc. drug

prophylaxis is mainly unfractionated heparin, low molecular weight heparin, vitamin K antagonists and new oral anticoagulants. The pharmacodynamic and pharmacokinetic characteristics of low molecular weight heparin are different from those of unfractionated heparin, such as good absorption, high utilization, long half-life, less adverse reactions and no need to monitor (7). Anticoagulants will increase the risk of bleeding, according to the mechanism of action has a specific choice, it is difficult to control the balance between hemostasis and anticoagulation (8). Traditional Chinese medicine therapy takes syndrome differentiation and treatment as the theoretical guidance, uses the whole concept to remove blood stasis and dredge collaterals, has less side effects, and is safer in combination with anticoagulants (9).

Mailuo Shutong granule is composed of Radix Astragali, Flos Lonicerae, Cortex Phellodendri, Atractylodes, Coix seed, Radix scrophulariae, Angelica, Radix Paeoniae Alba, licorice, leech, centipe. It has the effect of clearing heat and detoxification, removing blood stasis and dredging collaterals, removing dampness and detumescence. According to the results of clinical trials (10-13), Mailuo Shutong granule combined with low molecular weight heparin can effectively prevent postoperative DVT and may reduce the risk of bleeding with anticoagulants. However, there is no systematic evaluation of the efficacy and safety of Mailuo Shutong granule. The purpose of this study was to systematically evaluate the efficacy and safety of Mailuo Shutong granule combined with low molecular weight heparin in the prevention of postoperative DVT. Therefore, the efficacy and safety of Mailuo Shutong granule combined with low molecular weight heparin in the prevention of postoperative DVT were comprehensively evaluated by the method of Meta-analysis, so as to provide a basis for clinical decision-making.

We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/lcm-20-31>).

## Methods

### *Retrieval strategy*

PubMed, EMBase, Cochrane Library, China knowledge Network (CNKI), Wanfang Medical Database, Chinese Biomedical Literature Database (SinoMed), VIP data and other databases were searched by computer from the establishment of the database to July 2, 2020. Retrieval words including: (Mailuo Shutong granule OR Mailuoshutong) AND (deep venous thrombosis OR venous thromboembolism) AND (prevention) AND (randomized clinical trial OR randomized OR RCT). Retrieve completed but unpublished research on ClinicalTrials.gov and follow up the results.

### *Clinical trial inclusion criteria*

Trials were selected based on the following inclusion criteria: (I) Randomized controlled trial (RCT), with or without blind method. (II) In accordance with the diagnostic criteria of Chinese guidelines for the prevention and treatment of thrombotic diseases, the diagnosis of DVT should be combined with WELLS score, clinical manifestations, D-dimer test and auxiliary examination results, and comprehensive evaluation (14). (III) The experimental group was treated with Mailuo Shutong granule combined with low molecular weight heparin and mechanical prophylaxis, while the control group was treated with low molecular weight heparin and mechanical preventive therapy. (IV) Main outcome measures: incidence of DVT secondary outcome indicators: total clinical effective rate, incidence of adverse reactions. Exclusion criteria: (I) the patient has developed the DVT trial; (II) research on incomplete or unable to extract data; (III) repeatedly published research.

### *Literature screening and data extraction*

Two researchers, Tianyuan Wang and Jin Song, independently screened the literature according to the literature selection criteria, and combined with the characteristics of the literature included in this study, the literature information extraction table was developed. It mainly includes the following information: the name of the first author, the publication time, the sample size, the age of the subjects, the intervention measures, and the outcome index. In case of disagreement, consult Li Bo, a third-party

evaluator, and discuss it with Hong Wang and Shuo Feng.

### *Bias risk assessment*

Bias risk assessment and methodological quality assessment were carried out independently by Jing Hu and Huina Zhang. When there was disagreement, the opinions were unified through consultation with Bo Li.

According to the literature evaluation criteria (15) provided by Cochrane Handbook 5.3.0, the included studies were evaluated for bias risk, including the generation of random sequences, allocation hiding, blind evaluation of subjects and researchers, blind evaluation of study outcomes, integrity of outcome data, selective reporting of study outcomes and other biases. If each item is satisfied, it is low risk, if not satisfied, it is high risk, and if there is no sufficient information in the literature, the bias risk is unknown. Using inverted funnel chart to test publication bias.

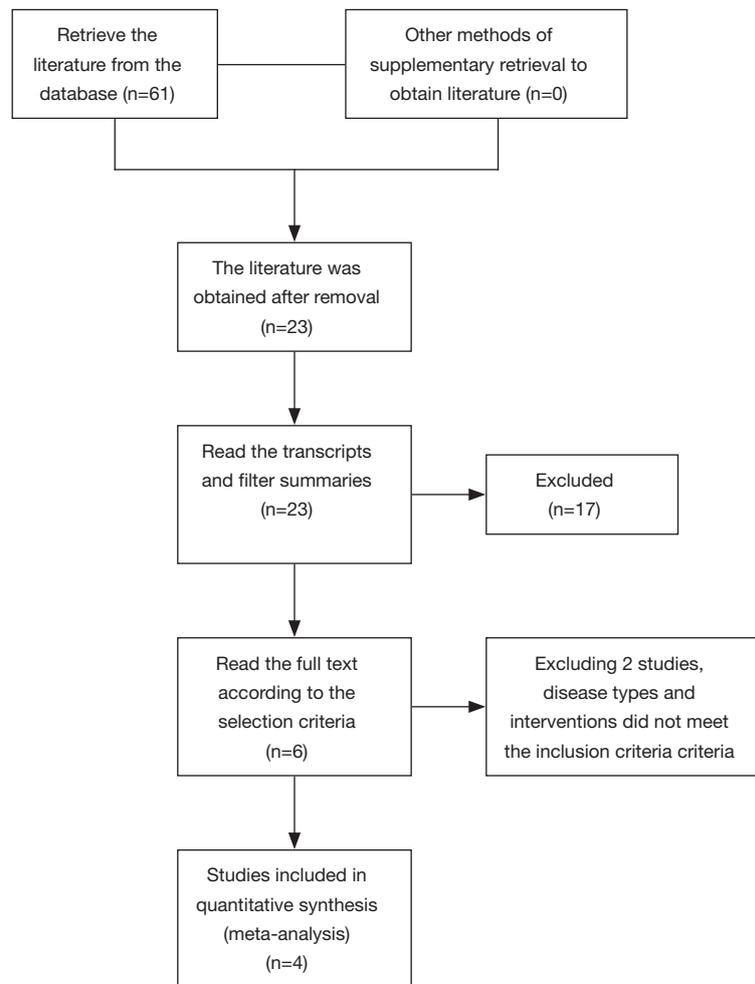
### *Statistical analysis*

RevMan 5.3 software was used for meta statistical analysis. The relative risk degree (RR) and 95% confidence interval (CI) were selected as the classification variables. The heterogeneity included in the study was judged by Q-value test (test level  $\alpha=0.05$ ) combined with  $I^2$ . When  $0 < I^2 \leq 50\%$ , it is considered that there is no obvious heterogeneity, so the fixed effect model is adopted. If  $I^2 \geq 50\%$ , it is considered that the heterogeneity is large, and the source of heterogeneity needs to be analyzed. The heterogeneity should be analyzed by subgroup analysis and sensitivity analysis. The patients were divided into different subgroups according to the patients or the type of intervention. If there is obvious statistical heterogeneity due to the different quality of the methodology included in the study, the low-quality study can be excluded for sensitivity analysis. When the clinical heterogeneity is not obvious, the random effect model is used.

## Results

### *Retrieval and screening of documents*

According to the retrieval strategy, 61 related articles were searched, including 0 articles of PubMed, 0 articles of Embase, 0 articles of Cochrane Library and 16 articles of China knowledge Network (CNKI), 15 articles of China



**Figure 1** Literature screening flow diagram.

Biomedical Literature Database (SinoMed), 11 articles of VIP Database, 19 articles of Wanfang Medical Database. No completed but unpublished studies were found. After the repetition is removed, the remaining 23 articles are left, and the remaining 6 articles are selected after the reading titles and abstracts are screened. The full text is selected according to the selection criteria and 4 articles are included. The specific literature screening process is shown in *Figure 1*.

#### ***The basic characteristics of the inclusion study***

A total of 4 articles (10-13) were included in this study, all of which were RCT studies. Four trials included 465 subjects. It mainly includes the following information: the name of the first author, publication time, sample size, age of study

subjects, intervention measures, outcome indicators. The basic features are shown in *Table 1*.

#### ***Include literature quality evaluation***

The main results are as follows: (I) random allocation method: random is mentioned in all studies, and random method is not described in all studies; (II) allocation scheme hiding: all studies have not designed allocation hiding method, blind method; (III) blindness to researchers and subjects: none of the studies blinded researchers and subjects; (IV) the blind evaluation of the study outcome: all the studies did not evaluate the study outcome by blind method; (V) the integrity of outcome data: the outcome data of all studies have integrity; (VI) selectively report the results of the study: none of the studies selectively reported

**Table 1** The basic features of the included study

Study	N (T/C)	Mean age		Interventions		Course of treatment (d)	Outcomes
		T	C	Treatment	Control		
Shi S, 2009	56/47	63.8±4.5	64.5±5.1	Mailuo Shutong granule combined with Low molecular weight heparin and Mechanical prophylaxis	Low molecular weight heparin combined with Mechanical prophylaxis	20	①②
Chen J, 2011	50/50	45.9±5.18		Mailuo Shutong granule combined with Low molecular weight heparin and Mechanical prophylaxis	Silibinin Capsules combined with conventional basic therapy	14	①②
Yao G, 2011	46/43	67.8±5.3	68.5±4.1	Mailuo Shutong granule combined with Low molecular weight heparin and Mechanical prophylaxis	Silibin Meglumine Tablets combined with conventional basic therapy	15	①
Zhang M, 2019	91/82	55±7	58±5	Mailuo Shutong granule combined with Low molecular weight heparin and Mechanical prophylaxis	Silibinin Capsules combined with conventional basic therapy	14	①

① Incidence of DVT; ② Harris hip score; ③ clinical efficacy rate; ④ adverse effects rate.

the results of the study; (VII) other sources of bias: no other bias was mentioned in all studies. Because of the small number of studies included, the inverted funnel diagram was not made. The quality evaluation of the methodology included in the study is shown in *Table 2*. Bias risk assessment, see *Figure 2*. Summary of bias risk, see *Figure 3*.

**Data analysis**

**Incidence of DVT**

A total of 365 patients were included in 3 (10-12) studies. The experimental group was treated with Mailuo Shutong granule combined with low molecular weight heparin and mechanical prophylaxis, while the control group was treated with low molecular weight heparin and mechanical preventive therapy. Heterogeneity test showed that there was low heterogeneity among the groups ( $P=0.76$ ,  $I^2=0$ ), and fixed effect model was used. The results showed that the effect of Mailuo Shutong granule combined with low molecular weight heparin and mechanical prophylaxis in reducing the incidence of postoperative DVT was better than that of low molecular weight heparin and mechanical prophylaxis (RR =0.47, 95% CI: 0.22–1.03,  $P>0.05$ ). The difference was not statistically significant, but there was a trend of change, and it may be statistically significant to increase the sample size (*Figure 4*).

**Incidence of adverse reactions**

A total of 273 patients were included in 2 (9,12) studies.

The experimental group was treated with Mailuo Shutong granule combined with low molecular weight heparin and mechanical prophylaxis, while the control group was treated with low molecular weight heparin and mechanical preventive therapy. Heterogeneity test showed that there was low heterogeneity among the groups ( $P=0.17$ ,  $I^2=0$ ), and fixed effect model was used. The results showed that the effect of Mailuo Shutong granule combined with low molecular weight heparin and mechanical prophylaxis in reducing the incidence of postoperative adverse reactions in the experimental group was better than that of low molecular weight heparin and mechanical prophylaxis (RR =0.63, 95% CI: 0.26–1.50,  $P>0.05$ ). The difference was not statistically significant, but there was a trend of change. See *Figure 5*.

**Total clinical effective rate**

One (9) study reported 100 patients. Fifty patients in the experimental group were treated with Mailuo Shutong granule combined with low molecular weight heparin and mechanical prophylaxis, while 50 patients in the control group were treated with low molecular weight heparin and mechanical prophylaxis. The results showed that the total effective rate of Mailuo Shutong granule combined with low molecular weight heparin and mechanical prophylaxis in the experimental group was 47%, while that of the control group was 35%, with a total effective rate of 35%. It is suggested that the total clinical effective rate of Mailuo Shutong granule combined with low molecular weight

Table 2 Quality evaluation of research methodology

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Shi S, 2009	Not mentioned	Unallocated hiding	The researchers and subjects were not blinded	No outcome blind evaluation was performed	Complete outcome data	Results were not selectively reported	Not mentioned
Chen J, 2011	Not mentioned	Unallocated hiding	The researchers and subjects were not blinded	No outcome blind evaluation was performed	Complete outcome data	Results were not selectively reported	Not mentioned
Yao G, 2011	Not mentioned	Unallocated hiding	The researchers and subjects were not blinded	No outcome blind evaluation was performed	Complete outcome data	Results were not selectively reported	Not mentioned
Zhang M, 2019	Not mentioned	Unallocated hiding	The researchers and subjects were not blinded	No outcome blind evaluation was performed	Complete outcome data	Results were not selectively reported	Not mentioned

heparin and mechanical prophylaxis on postoperative DVT in the test group is higher than that in the control group ( $P<0.05$ ). There was significant difference between the two groups ( $P<0.05$ ).

### Evaluation of GRADE evidence quality

The software GRADEprofiler3.6 was used to grade the evidence of each outcome index. The factors that affect the quality of evidence are described in detail in *Figure 6*.

## Discussion

### *The main findings of this study*

In recent years, the incidence of DVT in China is on the rise (16). The vast majority of patients have no obvious clinical symptoms, cannot be found and treated in time in the early stage of the disease, affecting patients' life and work, and may even lead to disability or sudden death (17). Early screening and prevention of DVT can effectively reduce the incidence of DVT. Optimizing the intervention measures for the prevention of DVT after operation can provide an effective scheme for clinical decision-making.

DVT is scattered in "swelling", "pulse arthralgia", "thigh swelling", "blood stasis flow" and other diseases. Most researchers believe that blood stasis blocking the veins is the basic pathogenesis of the disease (18).

Mailuo Shutong granule is composed of Radix Astragali, Flos Lonicerae, Cortex Phellodendri, Atractylodes, Coix seed, Radix scrophulariae, Angelica, Radix Paeoniae Alba, licorice, leech, centipe. Radix Astragali replenishes qi and solidifies the surface, tonifying qi, promoting blood circulation and removing blood stasis. Qi is the handsome of blood, Qi can carry blood, and the driving force of blood circulation is the promotion of Qi. Leeches break blood and expel blood stasis. Centipede dispels wind and relieves pain, attacks poison and disperses knots. The whole scorpion dredges collaterals to relieve pain. Honeysuckle and Cortex Phellodendri clear heat and purge fire and detoxify. Atractylodes dryness and dampness invigorates the spleen, dispels wind and dispels. Angelica tonifying blood and nourishing blood, Radix Paeoniae Alba promoting blood circulation to relieve pain. All kinds of medicines are compatible to play the effects of clearing heat and detoxification, removing blood stasis and dredging collaterals, removing dampness and detumescence.

Pharmacological studies show that Astragalus membranaceus can resist bacteria and viruses and dilate

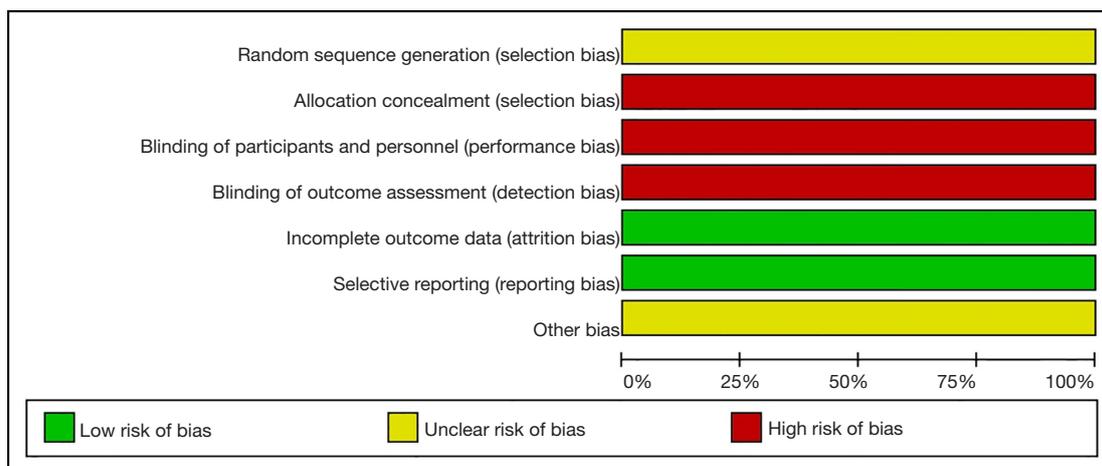


Figure 2 Risk of bias graph.

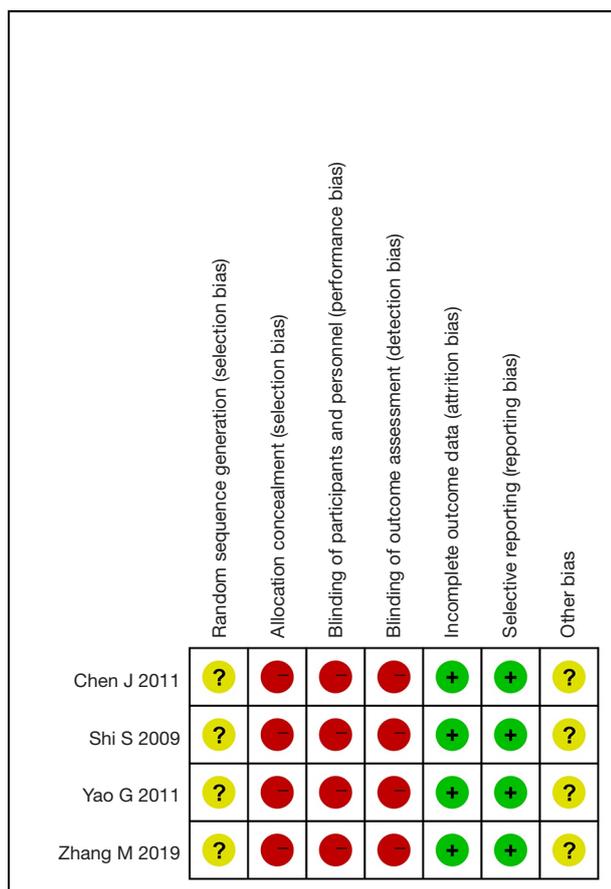


Figure 3 Risk of bias summary.

peripheral blood vessels to a certain extent (19). The salivary glands of leeches contain active substances that can improve tissue hyperalgesia and inhibit blood coagulation. it has the effect of thrombolysis and anti-platelet aggregation (20). Many studies have shown that hirudin is more effective in treating patients with DVT than heparin (21). The proteins and peptides contained in scorpion have anticoagulant effect (22). Centipede has anticoagulant effect, and centipede fibrinolytic enzyme has thrombolytic effect *in vivo* and *in vitro* (23). Flavonoids in Flos Lonicerae have strong antipyretic and anti-inflammatory effects, and organic compounds and triterpene soaps have good antibacterial and antiviral effects (24).

Finally, four RCT studies were included in this study. The results of Meta-analysis show that: (I) the trend of Mailuo Shutong granule combined with low molecular weight heparin in reducing the incidence of postoperative DVT may be better than that of low molecular weight heparin in reducing the incidence of postoperative DVT. (II) The trend of Mailuo Shutong granule combined with low molecular weight heparin in reducing the risk of bleeding with anticoagulants may be better than that of low molecular weight heparin in reducing the risk of bleeding with anticoagulants. (III) It has been reported that the clinical effect of Mailuo Shutong granule combined with low molecular weight heparin in the prevention of postoperative DVT may be better than that of low molecular weight heparin in the prevention of postoperative DVT.

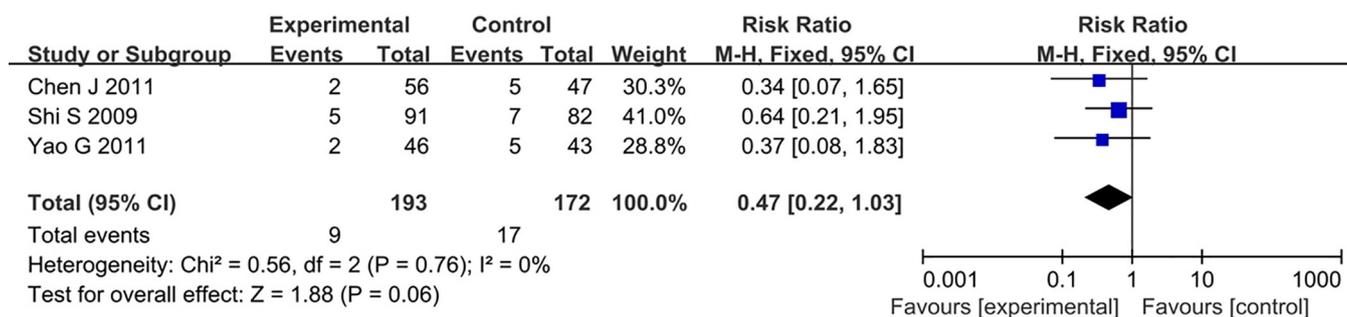


Figure 4 Forest plots of Incidence of deep venous thrombosis (DVT).

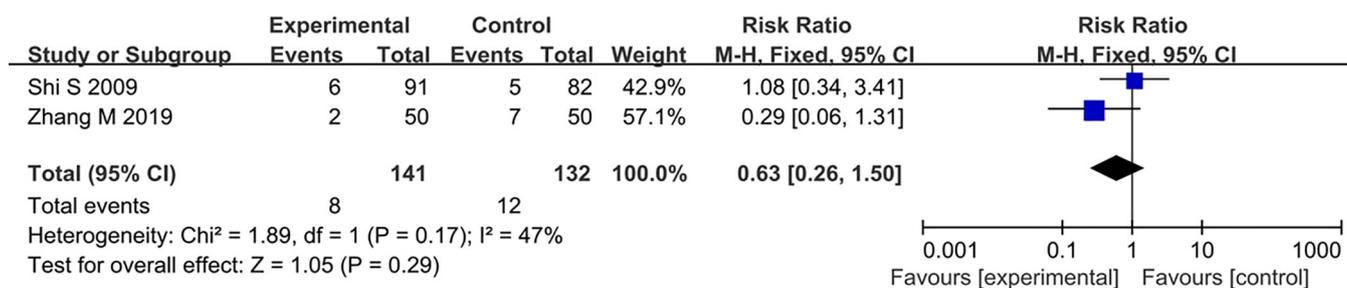


Figure 5 Forest plots of adverse effects rate.

### Limitations of the study

All the patients included in this study met the criteria for the possibility of DVT after operation, but the course of treatment included in the study was different, which was 20, 15, 14 and 14 days respectively. There were differences in the age range of patients, which may affect the results of the analysis. Try to ensure that the criteria included in the study are consistent to avoid clinical heterogeneity.

The control group was treated with low molecular weight heparin and mechanical prophylaxis. Two (10,13) studies did not mention the specific methods of mechanical prevention, which may affect the results of the analysis. The quality of the four studies included in this study is on the low side. According to the literature evaluation method, none of the four studies mentioned the random method, the implementation of hidden distribution, the blindness of the outcome evaluator, and the blind evaluation of the study outcome, which may have biased effects.

Comprehensive evaluation was included in the selection of outcome indicators of the study, including 4 studies. In terms of objective indicators, only 3 study outcome indicators selected the incidence of DVT, 2 study outcome

indicators selected the incidence of adverse reactions, and subjective outcome indicators did not choose clinical symptom scores as outcome indicators.

It is suggested that the large sample RCT test should be carried out in the future, and the researchers should strictly design the test scheme and strictly ensure the implementation quality, and should refer to the Cochrane risk bias assessment tool to improve the quality of the research methodology. In the choice of intervention measures, due to certain restrictions in the choice of anticoagulant low molecular weight heparin, it is easy to have complications such as anti-thrombocytopenia, bleeding and so on. According to the different suggestions of the operation site, we should pay attention to the new oral anticoagulant, such as Rivaroxaban, which can directly inhibit the production of thrombin and anticoagulant factor Xa, can effectively cut off the coagulation pathway and inhibit thrombosis. Intravenous active drugs such as diosmin can improve symptoms by reducing capillary permeability and reducing the release of inflammatory factors (25), so we can also focus on selecting the level of inflammatory factors as the outcome index. It is suggested that the objective

Main outcomes for prevention of postoperative deep venous thrombosis						
<b>Patient or population:</b> patients with prevention of postoperative deep venous thrombosis						
<b>Settings:</b>						
<b>Intervention:</b> Main outcomes						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Main outcomes				
Incidence of DVT	Study population		RR 0.47 (0.22 to 1.03)	365 (3 studies)	⊕⊕⊕⊕ very low <sup>1,2</sup>	
	99 per 1000	46 per 1,000 (22 to 102)				
	Moderate					
	106 per 1000	50 per 1,000 (23 to 109)				
<sup>1</sup> Risk of bias: Randomization was not mentioned in any of the three included studies; The blind method of allocation hiding method was not designed. None of the subjects were blinded; All the results were evaluated by blind method <sup>2</sup> The sample size is not calculated, and the confidence interval is wide						
Secondary outcomes for prevention of postoperative deep venous thrombosis						
<b>Patient or population:</b> patients with prevention of postoperative deep venous thrombosis						
<b>Settings:</b>						
<b>Intervention:</b> Secondary outcomes						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Secondary outcomes				
Incidence of adverse reactions	Study population		RR 0.63 (0.26 to 1.5)	273 (2 studies)	⊕⊕⊕⊕ very low <sup>1,2,3</sup>	
	91 per 1,000	57 per 1,000 (24 to 136)				
	Moderate					
	101 per 1,000	64 per 1,000 (26 to 152)				
<sup>1</sup> Risk of bias: Randomization was not mentioned in any of the three included studies; the blind method of allocation hiding method was not designed. None of the subjects were blinded; All the results were evaluated by blind method <sup>2</sup> Heterogeneity was detected between groups, P=0.17, I <sup>2</sup> =47 <sup>3</sup> The sample size is not calculated, and the confidence interval is wide						

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

**Figure 6** Evidence table of MaiLuo Shutong granule in the prevention of postoperative deep venous thrombosis. \*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, confidence interval; RR, risk ratio.

index should be the first choice as the outcome index, and the incidence of DVT should be chosen as the main curative effect index for clinical benefits. It is suggested that we should pay attention to the adverse reactions caused by the risk of anticoagulant bleeding, select the incidence of adverse reactions as the outcome index, choose the clinical symptom score as the outcome index, and establish a more

unified evaluation standard to make the research results more complete and more reliable.

### Conclusions

The trend of Mailuo Shutong granule combined with low molecular weight heparin in reducing the incidence

of postoperative DVT may be better than that of low molecular weight heparin in reducing the incidence of postoperative DVT, and there may be a tendency to reduce the risk of bleeding with anticoagulants. It has been reported that Mailuo Shutong granule combined with low molecular weight heparin may be superior to low molecular weight heparin in the prevention of postoperative DVT. It may be effective and safe to use prophylactic drugs for the occurrence of postoperative DVT, suggesting that clinicians can choose Mailuo Shutong granule combined with routine treatment in the prevention of postoperative DVT. However, the number of existing clinical studies is small and the quality is low, so it is recommended to use internationally recognized outcome indicators for further verification, and we need to pay attention to different types of therapeutic drugs. It needs to be confirmed by more high-quality clinical RCT tests.

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### Footnote

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*Ethical Statement:* The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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