Systematic Review and Meta-Analysis

Medicine

OPEN

Efficacy of traditional Chinese medicine combined with rivaroxaban in the treatment of lower extremity deep vein thrombosis

A meta-analysis

Dandan Zheng, BSN[a], Gui Qi, MMed[a,*], Isaac Kumi Adu, MBBS[a,b], Haichao Wu, MBBS[c], Mingyuan Zhu, BSN[a]

Abstract

Background: Despite the usefulness of traditional Chinese medicine (TCM) in the treatment of lower deep vein thrombosis (DVT), there is no consensus on safety and efficacy. We aim to systematically evaluate the safety and efficacy of TCM combined with Rivaroxaban in the treatment of lower limb DVT.

Methods: An online search of databases such as Cochrane Library, Embase, Pubmed, and Web of science, as well as CBM, China Science and Technology Journal Database, China Knowledge Network (CNKI) and Wanfang Data (from inception to July, 2021) was performed. All published clinical randomized controlled trials (RCTs) were screened manually, evaluated for quality and considered for meta-analysis using RevMan 5.3.

Results: Nine RCTs with a total of 730 cases were included, 368 cases in the trial group were treated with TCM combined with Rivaroxaban, and 362 cases in the control group were treated with Rivaroxaban alone after surgery. Clinical efficiency was significantly higher in the test group [OR = 3.33, 95% CI (2.01, 5.53), $P < .00001$], the circumference of the affected limb was significantly lower in the thigh and calf, respectively [MD = –1.48, 95% CI (–1.88, –1.09), $P < .00001$], [MD = –0.54, 95% CI (–0.62, –0.46), $P < .00001$], pain scores were significantly lower [MD = –0.97, 95% CI (–1.58, –0.36), $P = .002$], coagulation index plasma fibrinogen (FIB) was significantly lower [MD = –0.85, 95% CI (–1.18, –0.52), $P < .00001$], coagulation function index D-2 aggregates were significantly reduced [MD = –0.69, 95% CI (–1.13, –0.24), $P = .002$], serum hypersensitive C-reactive protein (hs-CRP) measurements were significantly reduced [MD = –5.37, 95% CI (–9.20, –1.55), $P = .006$], complications measurement was significantly lower [OR = 0.60, 95% CI (0.27, 1.30), $P = .20$], activated partial thrombin time (ATPP) measurement was significantly lower [MD = 5.70, 95% CI (4.28, 7.12), $P < .00001$] and prothrombin time (PT) measurement was significantly lower [MD = 1.64, 95% CI (0.70, 2.57), $P = .0006$].

Conclusion: Based on the available evidence, TCM combined with Rivaroxaban for treating lower extremity DVT have better clinical efficacy and safety profile, reducing the risk of bleeding complications and adverse effects. Further improved studies are needed to support this inference.

Abbreviations: ASH = American Society of Hematology, ATPP = activated partial thrombin time, DOACs = direct oral anticoagulant, DVT = deep vein thrombosis, FIB = coagulation index plasma fibrinogen, hs-CRP = hypersensitive C-reactive protein, PE = pulmonary embolism, PT = prothrombin time, TCM = traditional Chinese medicine, VTE = venous thromboembolism.

Keywords: lower limb deep vein thrombosis, meta-analysis, Rivaroxaban, traditional Chinese medicine.

1. Introduction

Venous thromboembolism (VTE), includes deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] It was reported that Approximately one-third of all patients newly diagnosed with VTE have PE, with or without DVT.[2] VTE refers to the abnormal clotting of blood in the venous lumen, so that the venous blood flow is obstructed, resulting in complete or incomplete blockage of blood vessels, It occurs mainly in the lower extremities.[3] Data from the American Society of Hematology (ASH) 2020 guidelines for the management of VTE (treatment of DVT and PE) showed that DVT occurred in at least 1 to 2 out of every 1000 people in the United States, with 300,000 to 600,000 events per year.[4] Some patients with DVT would

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

[a] Health Science Center, Yangtze University, Jingzhou, Hubei, China, [b] Department of Medicine, the Second Hospital of Jingzhou & the Affiliated Hospital of Hubei College of Chinese Medicine, Jingzhou, Hubei, China, [c] Department of Urology, The Second Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, China.

**Correspondence: Gui Qi, Health Science Center, Yangtze University, No. 1 Nanhuan Road, Jingzhou, Hubei 434023, China (e-mail: 2707684153@qq.com).*

How to cite this article: Zheng D, Qi G, Adu IK, Wu H, Zhu M. Efficacy of traditional Chinese medicine combined with rivaroxaban in the treatment of lower extremity deep vein thrombosis: A meta-analysis. Medicine 2022;101:39(e29483).

Received: 10 February 2022 / Received in final form: 29 April 2022 / Accepted: 3 May 2022

http://dx.doi.org/10.1097/MD.0000000000029483

progressively develop PE under the influence of multiple factors, which may result in death.[5] Therefore, the treatment and prevention of DVT should be of great concern. Novel oral anticoagulants are known to be most effective in the prevention and treatment of DVT but are associated with an increased frequency of bleeding complications. Major bleeding events may occur in 1%~3% of patients undergoing lower extremity surgery per year, but the relative risk of major bleeding is 30% lower compared to direct oral anticoagulant (DOAC).[6] The ASH VTE Treatment Guidelines Panel provided a conditional recommendation to replace VKA with DOAC as a treatment for patients newly diagnosed with VTE. DOAC does not require frequent dose adjustments, monitoring of international normalization ratio, or dietary restrictions and would be less burdensome for patients, especially during anti-coagulation therapy. For patients with DVT and/or PE who have completed primary therapy and continue to receive DOAC for secondary prevention, the ASH guideline panel recommended the use of standard-dose DOAC or lower-dose DOAC (based on moderate certainty of conditional recommendation in the evidence of impact AAA). For patients who have completed primary therapy and will continue to receive DOAC, low-dose DOAC regimens including rivaroxaban (10 mg daily) or apixaban (2.5 mg twice daily) may be considered.[7]

In recent years, more and more herbal medicines have obvious advantages in the treatment of thrombosis. Zhang et al[8] stated that herbal medicine has better efficacy, less complications and is economical than rivaroxaban treatment, and some scholars Sun Fei et al[9] believed that the efficacy of herbal medicine alone is the same as that of western medicine alone, with no significant difference in safety. So which is better, rivaroxaban combined with herbal medicine, compared to rivaroxaban alone? There is no specific one yet, and this is exactly what we need to know further.

In traditional Chinese medicine (TCM) theory, it is suggested that DVT belongs to the category of "pulse closure" and "femoral swelling", and the main treatment is to promote blood circulation and remove blood stasis.[10] TCM does not only have analgesic and anti-inflammatory effects but also can effectively improve blood circulation.[11]

Therefore, in performing the identification of TCM evidence, adjuvant treatment based on Western medicine treatment is increasingly emphasizing the TCM theory that diagnosis and treatment should be based on a comprehensive analysis of the patient's condition, and adherence to the primary and secondary aspects of the treatment of the disease. Therefore, the advantages of combining Chinese and Western medicine are becoming more prominent in the management of thrombotic diseases. We conducted this meta-analysis to evaluate the efficacy and safety of combining traditional Chinese medicine with rivaroxaban for the treatment of lower extremity DVT.

An explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).

1. Population, or participants and conditions of interest

People with VTE; any age, any gender and any severity of VTE. Population not restricted to the CHINA, will examine papers from all over the world.

2. Interventions or exposures

People who have been admitted to hospital with an exacerbation of VTE.
People treated with rivaroxaban drugs and Chinese traditional Medicines after the occurrence of VTE

3. Comparisons or control groups:

People who have been admitted to hospital of VTE.
People treated with rivaroxaban drugs after the occurrence of VTE.

4. Outcomes of interest:

① Clinical effect; ② Thigh weeks diameter; ③ Crus weeks diameter; ④ Pain score; ⑤ Coagulation function index FIB; ⑥ The coagulation function index D-D; ⑦ Hypersensitive C-reactive protein (hs-CRP); ⑧ complications; ⑨ Prothrombin time (PT); ⑩ Activated partial thrombin time.

5. Setting: Hospital admissions/Primary Care/secondary care
6. Study designs: Any study design; RCTs

2. Methods

This meta-analysis and systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[12] Ethical approval was waived, because of the nature of the study which only reviewed already published literature.

2.1. Search strategy, selection criteria, and outcomes

An online search of databases such as Cochrane Library, Embase, Pubmed, Web of science, and CBM, Chinese Science and Technology Journal Database, Wanfang Data, and China Knowledge Network (CNKI) from the database was built until July 2021. English search terms ([Rivaroxaban] OR [DVT in lower limbs] OR [Thrombosis of lower limb] OR [Venous thrombosis] OR [VTE] OR [DVT] OR [deep venous thrombosis] OR [Traditional Chinese medicine] OR [TCM] OR [Chinese Drugs] OR [Chinese Herbal Drugs] OR [integrative medicine]) were conducted using a combination of subject terms and free words for the search. Chinese search terms ([lower extremity DVT] OR [thrombosis] OR [Chinese medicine] OR [traditional Chinese medicine] OR [proprietary Chinese medicine] OR [Chinese herbal medicine] OR [combined traditional Chinese and Western medicine] OR [Rivaroxaban]) were also explored using a combination of subject words and free words. No language restriction was applied. The search strategy of the China Knowledge Network (CNKI) database is summarized in (Table 1).

Table 1

Search strategy used for the China Knowledge Network (CNKI) database.

Number	Search items
#1	Deep vein thrombosis in lower limbs [Title/Abstract] OR Thrombosis of lower limb [Title/Abstract] OR Lower extremity deep vein thrombosis [Title/Abstract] OR Thrombosis [Title/Abstract]
#2	Rivaroxaban [Mesh] OR Rivaroxaban Tablets [Mesh]
#3	#1 AND #2
#4	Chinese medicine [Mesh] OR traditional Chinese medicine [Mesh] OR proprietary Chinese medicine [Title/Abstract] OR Chinese herbal medicine, combined traditional Chinese and Western medicine [Mesh] OR Chinese Drugs [Title/Abstract] OR integrative medicine [Mesh] OR TCM [Title/Abstract]
#5	#3 AND #4
#6	Randomized Controlled Trials as topic [Mesh] OR Clinical Trials, Randomized [Title/Abstract] OR Controlled Clinical Trials, Randomized[Title/Abstract] OR Randomized Controlled Trial [Publication Type] OR Intention to Treat Analysis [Mesh] OR Controlled Clinical Trials as Topic [Mesh]
#7	#5 AND #6

TMC = traditional Chinese medicine.

All published studies on patients with diagnosed lower limb DVT with the following features were considered eligible for the meta-analysis: Randomized controlled trials (RCTs) and post hoc analysis of RCTs; clearly reported efficacy and/or safety of Chinese herbal medicine combined with Rivaroxaban in the treatment of lower limb DVT (trial group); if results on the efficacy and/or safety of only Rivaroxaban treatment of lower limb DVT (as a control group) were markedly reported. Non-RCTs, duplicate published literature, control groups including traditional Chinese medicine treatments, literature with missing important information that prevented data extraction, and reviews, case reports, conference reports, systematic reviews, abstract articles, review articles, animal or cadaver studies, or articles published as non-clinical trials were excluded.

Two investigators (ZDD and AKI) independently searched and screened the relevant literature according to the Inclusion and exclusion criteria, by reading the titles as well as the abstracts, and requested full-text reading if they could not be identified. The full text of all articles with potentially relevant abstracts was retrieved and screened according to the inclusion and exclusion criteria of the study. Disagreements were adjudicated by a third investigator (WHC).

2.2. Data extraction and quality assessment

Extraction of data was performed by two investigators (ZDD and AKI). They reviewed the titles and abstracts, read the full text carefully according to the pre-defined inclusion criteria, and extracted data from the included studies using a pre-designed data extraction form. Extracted data characteristics included authors, year of publication, sample size, age of subjects, and details of both groups, outcome measures, summary of results, main findings, and adverse effects. The extracted data were cross-checked by 2 investigators (ZDD and AKI) after collection. Data were arranged in experimental form and Excel spreadsheets in duplicate. All data extraction was done independently by both investigators (ZDD and AKI). When any inconsistencies arose, a third investigator (WHC) adjudicated.

The quality of the literature was evaluated by 2 investigators (ZDD and AKI) using the seven items recommended by the Cochrane Systematic Review for Risk of Bias Assessment.[13] The assessment included a "yes", "no", or "unclear" judgment for each domain, signifying low, high, or unclear risk of bias, respectively.[13] Any disagreement was resolved through discussion or judgment by a third investigator (WHC).

2.3. Statistical analysis of data

All statistics were analyzed using Review Manager software (RevMan version 5.3, the Cochrane Collaboration Centre, Copenhagen). Continuous variables were expressed as mean ± standard deviation (SD) and assessed by mean difference (MD). Categorical data were expressed as percentages (%) and analyzed to calculate the relative risk (RR) or dominance ratio. Chi-square test (χ^2) and I^2 test were used to assess the heterogeneity of the clinical trial data and to determine the appropriate model for analysis (fixed-effects model or random-effects model). Heterogeneity was defined as acceptable when the χ^2 test P value was <.05 and I^2 test value was <50%, When heterogeneity is not obvious, a fixed-effects model can be used to estimate the combined effect size; if heterogeneity exists and the theoretical effect size is assumed to be not fixed and obey some distribution, such as normal distribution, a random-effects model can be chosen; if heterogeneity is too obvious, subgroup analysis, meta-regression or even abandoning the combination and only statistical description of the results should be considered. For each included study, a weighted mean difference with 95% confidence interval (CI) was calculated for continuous outcomes, while a ratio (OR) with 95% confidence interval (CI) was calculated for dichotomous outcomes. The ratio (OR) and 95% CI were used to express the continuous variables in the evaluation index.

3. Results

3.1. Study selection, quality of evidence, and patients' characteristics

Eight hundred eighty literature were initially examined (Fig. 1), all in Chinese except for 12 English literature, was retrieved. A total of 502 literature remained after excluding duplicate literature, 10 literature remained after excluding other interventions and incomplete data by reading the label data and abstract. After excluding non-RCTs and literature for which valid data could not be extracted by reading the full text, 9 literature met the inclusion criteria finally, all of which were RCTs, and the studies were consistent at baseline. A total of 730 cases were included in the 9 RCTs studies, including 368 cases in the trial group (Chinese herbal medicine combined with Rivaroxaban treatment group) and 362 cases in the control group (rivaroxaban alone group). The 2 investigators reached 100% agreement on the data extraction.

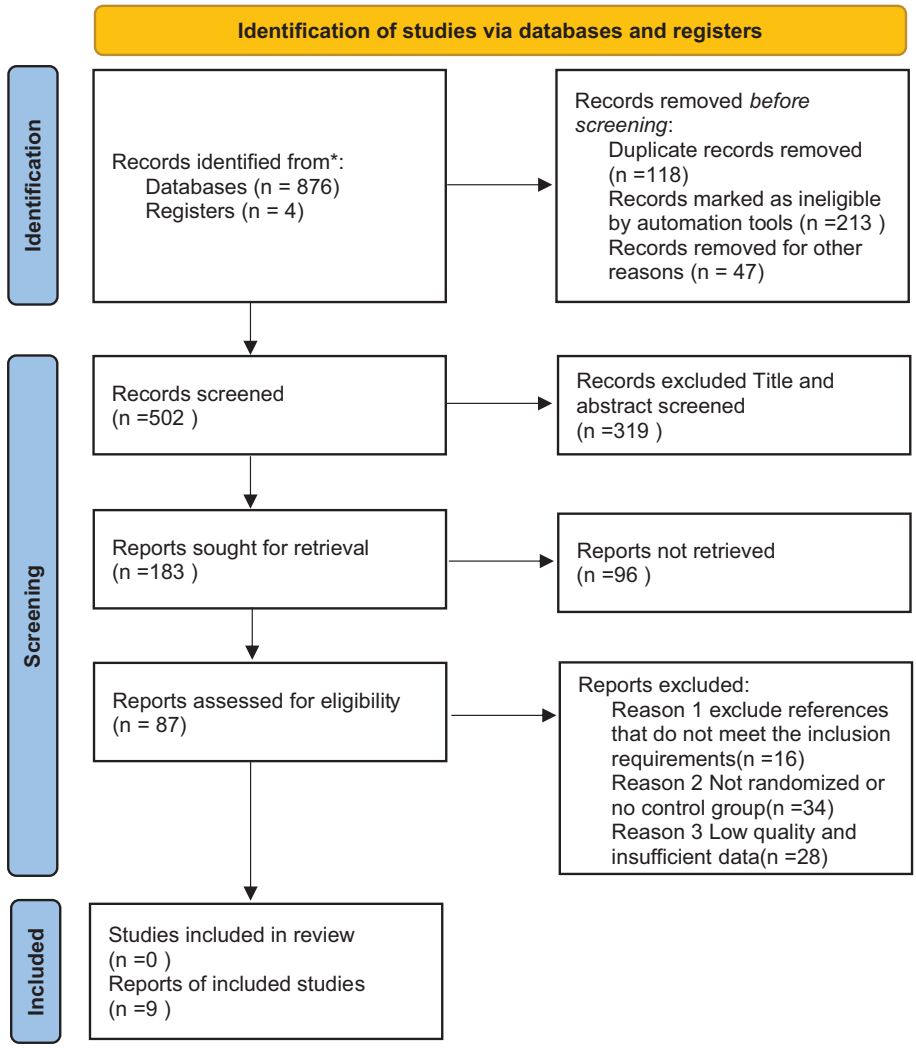
The results showed that all included studies mentioned "randomization", 2 mentioned random number table method, 1 mentioned random number method, 1 mentioned random classification method to generate random numbers, and the rest of the literature did not mention specific randomization methods; 7 literature did not mention whether the allocation scheme was hidden; In 2 literature, the prognostic events were not observed enough, and 1 literature did not report comprehensive and insufficient information for the principal investigator to judge; 2 literature did not explicitly report the number of missed visits, dropouts, and whether intentional analysis was conducted (Fig. 2). The general characteristics of the literature are shown in (Table 2).

3.2. Efficacy and safety of lower limb DVT treatment

A total of 8 papers dealt with the clinical efficiency after DVT treatment, with a total of 501 patients, 251 in the test group and 250 in the control group. After the heterogeneity test, the clinical efficiency after DVT treatment ($\chi^2 = 1.83$, $P = .97$, $I^2 = 0\%$), there was no heterogeneity among the trial group, and the fixed-effect model was used. The results showed that there was a statistically significant difference in the clinical effective rate between the 2 groups (OR = 3.33, 95% CI [2.01, 5.53], $P < .00001$), suggesting that herbal medicine combined with rivaroxaban treatment can effectively treat DVT (Fig. 3).

Only 3 studies reported on the thigh circumference score of the treated patients with a total of 296 patients, 148 in the trial group and 148 in the control group. After testing for heterogeneity, there was no heterogeneity between the study groups in the treated affected limb circumference scores ($\chi^2 = 18.96$, $P < .0001$, $I^2 = 89\%$), using a fixed-effect model. The results showed that the difference in affected limb circumference was compared with no statistically significant difference (MD = –1.48, 95% CI [–1.88, –1.09], $P < .0001$), suggesting no significant effect of combined herbal treatment on affected limb circumference (Fig. 4).

Exclusively, 3 studies reported on the calf circumference score of the treated patients with a total of 296 patients, 148 in the trial group and 148 in the control group. After testing for heterogeneity, there was no heterogeneity between the study groups in the treated affected limb circumference scores ($\chi^2 = 11.45$, $P = .003$, $I^2 = 83\%$), using a fixed-effect model. The results showed that the difference in affected limb circumference was compared



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

with no statistically significant difference (MD = −0.54, 95% CI [−0.62, −0.46], $P < .00001$), suggesting no significant effect of combined herbal treatment on affected limb circumference (Fig. 5).

Postoperative pain scores were reported in only 3 studies, for a total of 223 patients, 112 in the test group and 111 in the control group. After testing for heterogeneity, postoperative pain scores ($\chi^2 = 17.05$, $P = .0002$, $I^2 = 88\%$), there was heterogeneity between the study groups, using a random effects model. The results showed no statistically significant difference in postoperative pain scores between the two groups (MD = −0.97, 95% CI [−1.58, −0.36], $P = .002$). It was suggested that combined herbal treatment had no significant effect on postoperative pain scores (Fig. 6).

Five studies reported on the coagulation function indicator plasma fibrinogen (FIB) in a total of 442 patients, 224 in the test group and 218 in the control group. After testing for heterogeneity, the coagulation function index plasma FIB ($\chi^2 = 40.0$, $P < .00001$, $I^2 = 90\%$), there was heterogeneity between the study groups, using a random-effects model. The results showed no statistically significant difference in plasma FIB, an index of coagulation function, between the 2 groups after surgery (MD = −0.85, 95% CI [−1.18, −0.52], $P < .00001$), suggesting that combined herbal treatment had no significant effect on plasma FIB, an index of coagulation function (Fig. 7).

Three studies reported coagulation function index D-2 aggregates in a total of 229 patients, 115 in the test group and 114 in the control group. After testing for heterogeneity, coagulation function index D-2 aggregates ($\chi^2 = 20.42$, $P < .0001$, $I^2 = 90\%$), there was heterogeneity between the study groups, and a random-effects model was used. The results showed that the coagulation function index D-2 aggregates were significantly lower in the test group,and the difference was statistically significant (MD = −0.69, 95% CI [−1.13, −0.24], $P = .002$), suggesting that combined herbal treatment had no significant effect on postoperative coagulation function index coagulation function index D-2 aggregates (Fig. 8).

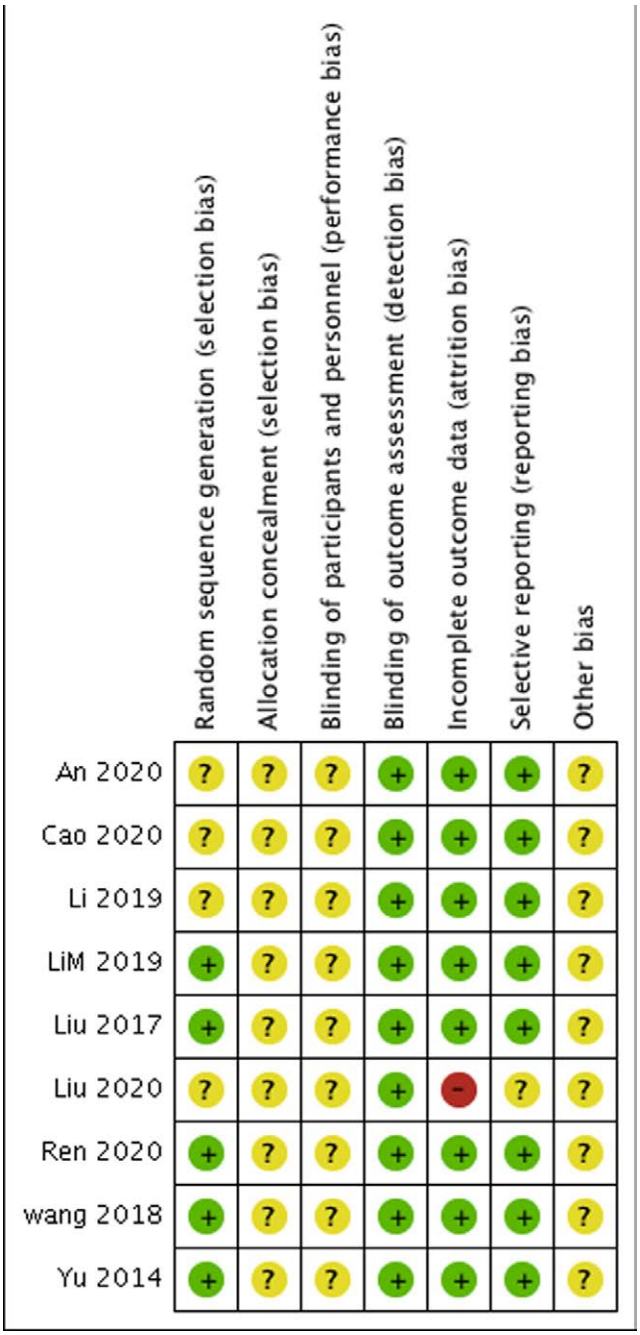


Figure 2. Risk bias assessment for included studies.

The results of serum hs-CRP assay were reported in three studies, with a total of 241 patients, 121 in the trial group and 120 in the control group. After testing for heterogeneity, serum hs-CRP assay results ($\chi^2 = 77.50$, $P < .00001$, $I^2 = 97\%$), there was heterogeneity between study groups, and a random-effects model was used. The results showed that the serum hs-CRP assay results in the test group were lower than those in the control group, and the difference was statistically significant (MD = –5.37, 95% CI [–9.20, –1.55], $P = .006$), suggesting that the serum hs-CRP assay results were significantly lower after anti-coagulation treatment with Chinese medicine combined with rivaroxaban (Fig. 9).

The number of adverse reactions and complications were reported in 4 studies, with a total of 354 patients, 180 in the trial group and 174 in the control group. After testing for heterogeneity, the number of adverse reactions and complications ($\chi^2 = 5.25$, $P = .26$, $I^2 = 24\%$), there was no heterogeneity between the study groups, and a fixed-effects model was used. The results showed that the no difference in the number of adverse reactions and complications between the 2 groups was statistically significant (OR = 0.60, 95% CI [0.27, 1.30], $P = .20$) (Fig. 10).

The number of activated partial thrombin time (APTT) was reported in 3 studies, with a total of 290 patients, 145 in the trial group and 145 in the control group. After testing for heterogeneity, the number of APTT ($\chi^2 = 3.68$, $P = .16$, $I^2 = 46\%$), there was no heterogeneity between the study groups, and a fixed-effects model was used. The results showed that the difference in the number of adverse reactions and complications between the 2 groups was statistically significant (MD = 5.70, 95% CI [4.28, 7.12], $P < .00001$), suggesting that the number of adverse reactions and complications was significantly lower after anti-coagulation with herbal medicine combined with Rivaroxaban (Fig. 11).

The number of PT was reported in 3 studies, with a total of 290 patients, 145 in the trial group and 145 in the control group. After testing for heterogeneity, the number of PT ($\chi^2 = 36.38$, $P < .00001$, $I^2 = 92\%$), there was no heterogeneity between the study groups, and a fixed-effects model was used. The results showed that the difference in the number of adverse reactions and complications between the 2 groups was statistically significant (MD = 1.64, 95% CI [0.70, 2.57], $P = .0006$), suggesting that the number of adverse reactions and complications was significantly lower after anti-coagulation with herbal medicine combined with rivaroxaban (Fig. 12)

4. Discussion

Intraoperative bleeding and postoperative thrombosis have always been two major challenges physicians are faced with. As early as the mid-19th century, Virchow proposed three main factors for thrombosis: blood flow velocity, vessel wall damage, and blood hyper-coagulation. The veins of the lower extremities are thick and farthest from the heart, therefore, blood flows more slowly, favoring clot and thrombus formation. Currently, the incidence of DVT is increasing year by year, and its cause is mainly due to thrombosis. If diagnosis and treatment are not timely or inaccurate, it can result in critical complications such as post-thrombotic sequelae or PE. Fatal PE has a very low success rate of resuscitation without any aura and is one of the most common causes of death outside the hospital. Anti-coagulation is the early standard of care for lower limb DVT and an important method for preventing perioperative thrombosis. There are various anticoagulant drugs on the market, and the common ones are low molecular weight heparin, warfarin and rivaroxaban.

Rivaroxaban, as a new oral anticoagulant drug, can precisely select and combine factor X and prothrombin activity, so that partial PT and PT can be activated and continued. The difference between rivaroxaban and these two conventional drugs is that, heparin is ineffective against the major factors within prothrombin and cannot act alone; anti-coagulation can only be achieved with the action of antithrombin III.[15,17] In addition, there are limitations to the use of warfarin, as the dose must be adjusted by constant monitoring of coagulation to achieve the desired effect. For example, the therapeutic window is narrow and it can interact with certain foods or drugs.[18] However, rivaroxaban does not require the involvement of antithrombin III and can directly antagonize free and bound factor Xa to effectively interrupt exogenous and endogenous coagulation pathways to inhibit thrombus formation.[16] It has the advantages of simple administration, high safety, low complication rate and no need for routine coagulation monitoring.[14] This makes it widely used in clinical practice. Meanwhile, in terms of long-term efficacy, the use of rivaroxaban has also reduced the disability and

Table 2

The basic characteristics of included studies

Study	Study quality	Combination group			Control group			Outcome indicators
		Sample size	Treatment measures	Age	Sample size	Treatment measures	Age	
An Y (2020)[14]	RCT	35	Qili powder acupoint application + Rivaroxaban	63 ± 11	35	Rivaroxaban	45.95 ± 10.27	①②③④⑤
Li WY (2019)[15]	RCT	44	Ginkgo damo injection + Rivaroxaban	62.19 ± 4.26	44	Rivaroxaban	61.36 ± 3.18	①②③⑤⑥
Liu Q (2017)[11]	RCT	33	Qingying Cooling Blood stasis soup + Rivaroxaban	54.92 ± 7.69	33	Rivaroxaban	55.89 ± 8.6	①⑦⑧
Ren Y (2020)[16]	RCT	32	Yiqi anti - embolic pill + Rivaroxaban	56.7 ± 15.5	27	Rivaroxaban	57.7 ± 16.5	①②③⑤⑧⑨⑩
Wang J (2020)[10]	RCT	44	Salvia miltiorrhiza ligustrazine injection + Rivaroxaban	48.2 ± 7.0	43	Rivaroxaban	49.1 ± 7.2	①④⑥⑦⑧
Yu ZH (2014)[17]	RCT	35	Danhong injection + Rivaroxaban	20–93	35	Rivaroxaban	20–93	①⑨⑩
Liu SN (2020)[1]	RCT	32	External application of xiaoshuan tongluo ointment + Rivaroxaban	48.5 ± 17.5	32	Rivaroxaban	48.6 ± 16.2	⑤⑧
Li MX (2019)[1]	RCT	75	Traditional Chinese medicine formula + Rivaroxaban	68.43 ± 5.70	75	Rivaroxaban	68. 43 ± 5. 70	①④⑤⑥⑦⑧⑨
Cao J (2020)[1]	RCT	38	Mai Tong SAN external application + Rivaroxaban	58.37 ± 6.43	38	Rivaroxaban	58. 46 ± 6.29	①

① Clinical effect; ② Thigh weeks diameter; ③ Crus weeks diameter; ④ Pain score; ⑤ Coagulation function index FIB; ⑥ The coagulation function index D-D; ⑦ Hypersensitive C-reactive protein (hs-CRP); ⑧ complications; ⑨ Prothrombin time; ⑩ Activated partial thrombin time.

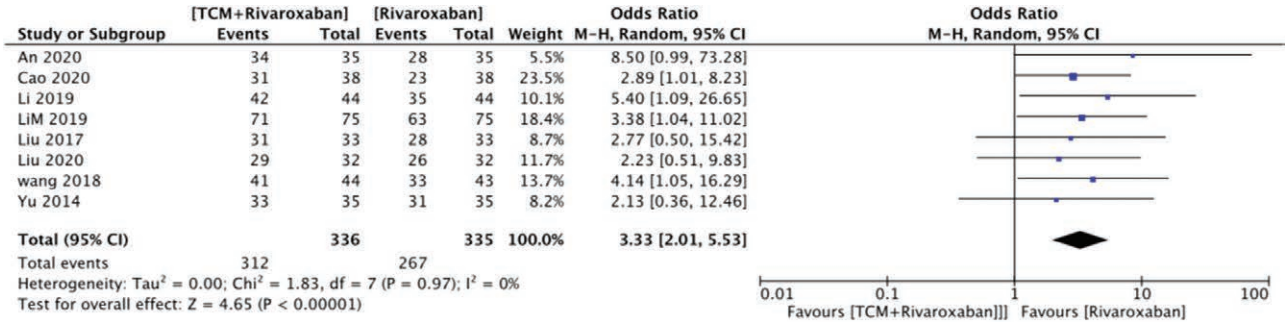


Figure 3. The clinical effective rate.

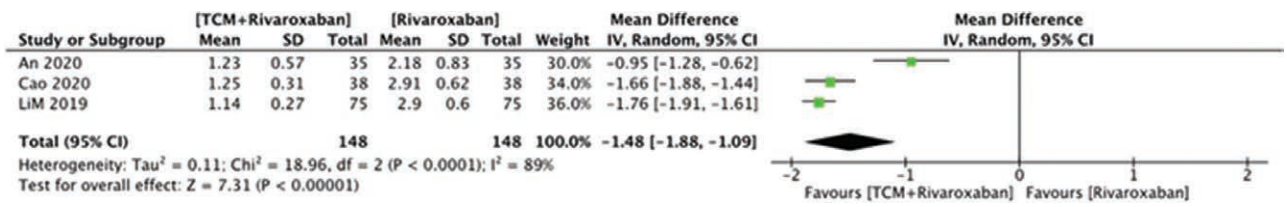


Figure 4. The thigh circumference score.

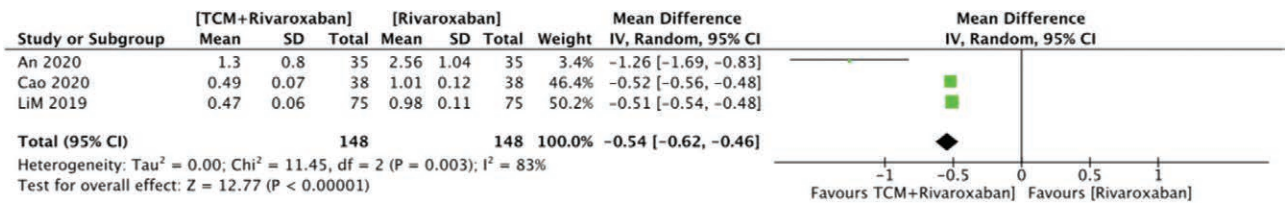


Figure 5. The calf circumference score.

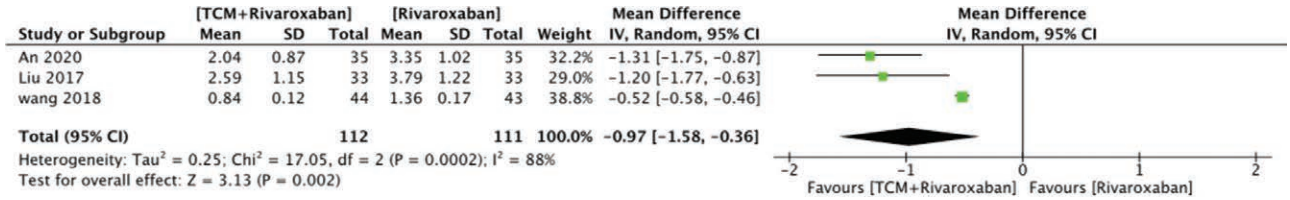


Figure 6. The postoperative pain scores.

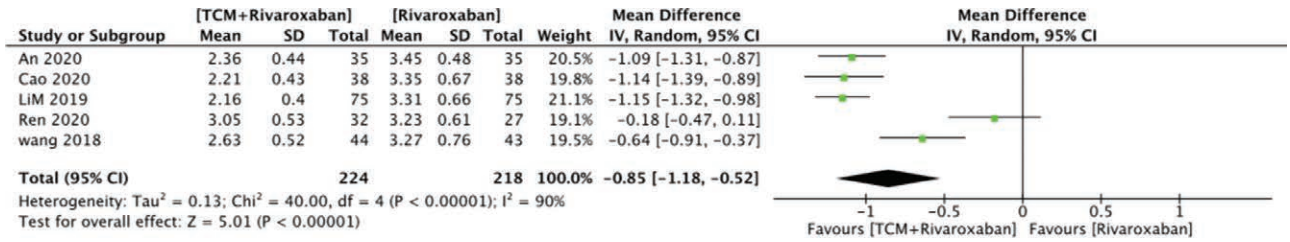


Figure 7. The coagulation function indicator plasma fibrinogen (FIB).

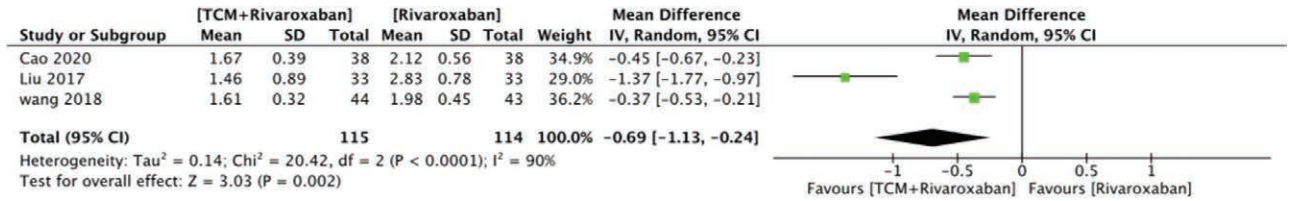


Figure 8. The coagulation function index D-2 aggregates.

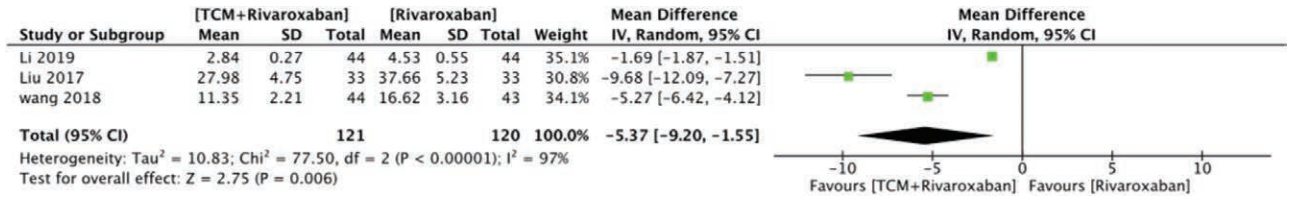


Figure 9. The serum hs-CRP assay.

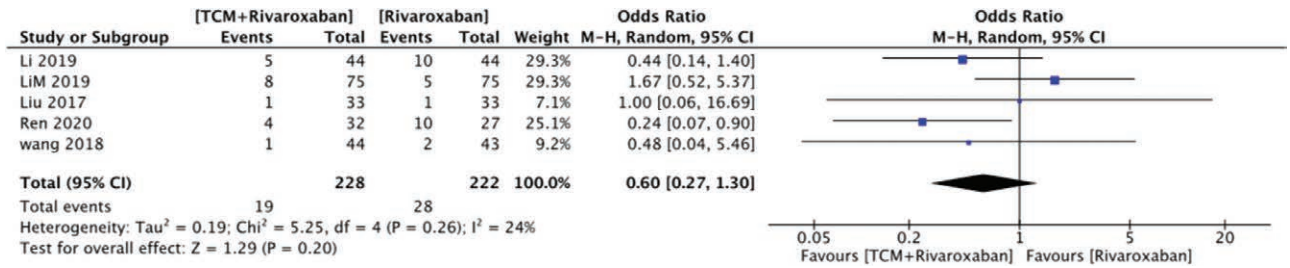


Figure 10. The adverse reactions and complications.

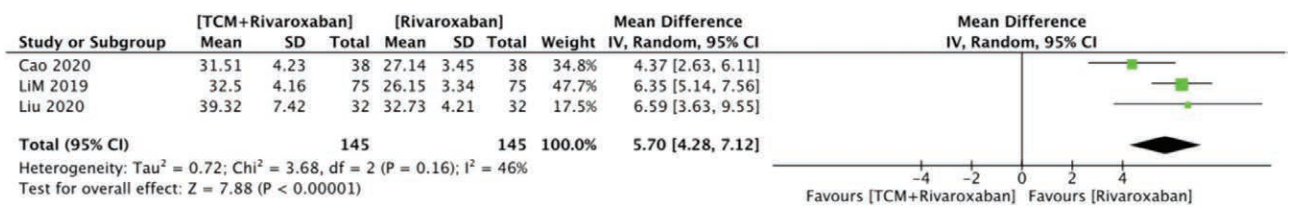


Figure 11. The activated partial thrombin time (APTT).

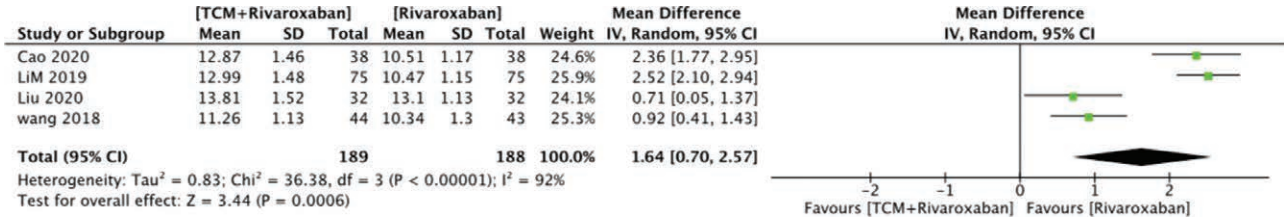


Figure 12. The number of PT.

mortality rates of patients to a certain extent, and has gradually become a routine choice of anti-coagulation regimen.

In recent years, anti-coagulation protocols under the combination of Chinese and Western medicine have been widely recognized in the treatment of lower extremity DVT and have also received evidence-based support from many randomized clinical trials.[19–25] Most Western scholars may consider Chinese herbal medicine, also known as TCM, not as a science but as an experience, and without any theoretical basis to support it. However, in fact, the use of herbal medicine to prevent and treat thrombosis has been practiced in China for more than a thousand years. It has its own unique advantages. There is growing evidence that TCM has unique advantages in the prevention of DVT and has been successfully applied to patients with DVT.[26] Herbal formulas not only have good efficacy in reducing swelling and stopping bleeding, but also have the effect of promoting blood circulation to eliminate obstruction of the patient's channels.[27] Moreover, herbal medicines can also protect vascular endothelium through multi-target modulation.[28] Our study included a total of 9 studies involving 730 patients. All studies included were RCTs.

The outcome of the meta-analysis showed that the combination of Chinese and Western medicine had significant advantages in the treatment of lower extremity DVT. In the nine randomized controlled trials included, the most commonly used herbs for the treatment of DVT included: Salvia miltiorrhiza, Chuanxiong rhizome,Yimou herb, Safflower, leech, Ginkgo biloba, Astragalus, Panax notoginseng, Radix Codonopsis, and Angelicae Sinensis. Among them, Danshen and Chuanxiong have pharmacological effects such as anti-platelet aggregation, reducing blood viscosity, improving micro-circulation, anti-coagulation, regulating blood lipids, antioxidant, and increasing the flow rate of red blood cells.[29] Yi Mu Cao can remove blood stasis and relieve pain by activating blood circulation and promoting menstruation.[30] Ginkgo biloba can effectively inhibit platelet-activating factor-mediated platelet coagulation and remove intravascular lipid accumulation.[19,31,32]

Safflower and angelica are effective in activating blood flow and eliminating blood stasis. Safflower has a vasodilation effect, and its yellow pigment component inhibits platelet aggregation and increases fibrinolytic enzyme activity, which significantly prolongs whole blood coagulation time and plasma re-calcification time, and has anticoagulant and anti-thrombotic effects.[33] Salvia miltiorrhiza can increase fibrinolytic enzyme activity by promoting fibrinolysis and inhibiting platelet aggregation.[33] This then improves the rheological properties of patients with blood stasis, and have an anti-thrombotic effect. DVT is in the category of "blood stasis" and "pulse paralysis" in Chinese medicine, so the method of activating blood and removing stasis from blood is the main treatment principle.[10] In summary, these herbal medicines are useful in the treatment of lower limb DVT.

This study intends to analyze the effectiveness and safety of Chinese herbal medicine combined with rivaroxaban in the treatment of patients with lower extremity DVT by means of meta-analysis.

A total of 9 studies were included, with a total of 730 observers. There were 368 cases in the test group, in which the intervention was postoperative treatment with herbal medicine combined with rivaroxaban, and 362 cases in the control group, in which the control measure was postoperative treatment with rivaroxaban only. The results showed that in terms of safety and efficacy, compared with rivaroxaban alone, the clinical efficacy of the Chinese herbal medicine combined with rivaroxaban group was significantly improved, the circumference score of the affected limb was significantly reduced, the pain score was significantly reduced, as well as the plasma viscosity. Plasma FIB, an index of coagulation function, the serum hs-CRP measurement, and the D-2 aggregates, an index of coagulation function, were all reduced significantly. The number of adverse reactions and complications was reduced, and the difference was statistically significant. This results denotes that Chinese medicine and rivaroxaban have a synergistic anticoagulant effect. The combination can help achieve better clinical efficacy in the treatment of lower limb DVT, not only reduce the risk of bleeding, but also complications and adverse reactions, with high effectiveness and safety. In terms of various coagulation indexes, the difference between Chinese herbal medicine combined with rivaroxaban group and rivaroxaban alone was not statistically significant, indicating that the combined use of Chinese herbal medicine does not affect its own coagulation function and does not increase bleeding tendency, which illustrates the therapeutic advantages of herbal interventions. This can promote the balance of bleeding and anti-coagulation, thus reducing complications.

We acknowledge some potential limitations that should be considered in this study. First, although adequate databases have been systematically searched, the number of included literature and the sample size of these studies are small and the statistical efficiency may be insufficient. Secondly, the differences in TCM prescriptions and treatment procedures used in each study are influenced by different factors, and the number of sample included in each study is relatively small. The study failed to further explore the sources of heterogeneity and parallel subgroup analysis was not published.

Chinese medicine has been practiced in China for thousands of years and has formed a set of its own medical theory system.[34] However, with the development of modern China, some of research on TCM theory has deep thinking. Most physicians are skeptical of the use of TCM, except for Chinese medicine practitioners. In selecting anticoagulants for DVT prevention, TCM doctors have developed some drugs using their own theoretical systems. Although some success has been achieved in clinical applications, these studies are scattered and independent. The lack of systematic research has limited the use and development of herbal anticoagulant drugs. Future studies should focus on promoting the development of herbal anticoagulants and providing a systematic analysis of the functions and characteristics of herbal anticoagulants.

In conclusion, with the current evidence, the application of Chinese herbal medicine combined with rivaroxaban have synergistic anti-coagulation effects in patients diagnosed with lower extremity DVT can effectively improve the anti-coagulation effect, reduce the risk of complications and increase the safety

of treatment, hence it is recommended for clinical application. However, the shortcomings of this study including the limited level of evidence in the included literature and the methodological refinement, and omissions are inevitable. More high-quality studies with large samples of RCTs are needed to increase the reliability of the results.

Author contributions

Formal analysis: Haichao Wu.
Funding acquisition: Gui Qi.
Investigation: Dandan Zheng.
Methodology: Haichao Wu.
Project administration: Gui Qi, Mingyuan Zhu.
Software: Dandan Zheng, Isaac Kumi Adu.
Supervision: Gui Qi.
Validation: Isaac Kumi Adu, Mingyuan Zhu.
Writing – original draft: Dandan Zheng.
Writing – review & editing: Dandan Zheng, Isaac Kumi Adu.

References

[1] Delluc A, LeMao R, Tromeur C, et al. Incidence of upper -extremity deep vein thrombosis in western France: a community-based study. Haematologica. 2019;104:e29–31.
[2] Cushman M, Tsai AW, White RH, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med. 2004;117:19–25.
[3] Grant JD, Stevens SM, Woller SC, et al. Diagnosis and management of upper extremity deep-vein thrombosis in adults. Thromb Haemost. 2012;108:1097–108.
[4] Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12:464–74.
[5] Huang W, Golberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985-2009). Am J Med. 2014;127:829–839.e5.
[6] Piran S, Schulman S. Treatment of bleeding complications inpatients on anticoagulant therapy. Blood. 2019;133:425–35.
[7] Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020;4:4693–738.
[8] Shen D. Effect of Taohong Siwu decoction on postoperative swelling, D-dimer and fibrinogen of femoral intertrochanteric fracture [D]. Zhejiang University of Chinese Medicine; 2019.
[9] Sun Q, Tang Z, Jiang S. Clinical observation of Qushangling in prevention of deep venous thrombosis of lower extremity after hip fracture. Chin J Integr Trad Western Med. 2019;31:1463–5.
[10] Li P, Liao R, Luo T, et al. Clinical study of Yiqi Huoxue Tongmai Prescription in prevention of deep vein thrombosis after knee replacement. Chin New Drugs Clin Pharmacol. 2019;2:268–73.
[11] Gu Y, Zheng L, Xiao L-bo, et al. Clinical efficacy of Traditional Chinese medicine in prevention of deep vein thrombosis after knee arthroplasty in rheumatoid arthritis. Chin J Integr Tradit West Med. 2019;39:1050–5.
[12] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
[13] Knobloch K, Yoon U, Vogt PM. Preferred reporting items for systematic reviews and meta- analyses (PRISMA) statement and publication bias. J Craniomaxillofac Surg. 2011;39:91–2.
[14] Gulseth MP, Michaud J, Nutescu EA. Rivaroxaban: an oral direct inhibitor of factor Xa. Am J Health Syst Pharm. 2008;65:1520–9.
[15] Weitz JI, Linkins LA. Beyond heparin and warfarin: the new generation of anticoagulants. Expert Opin Investig Drugs. 2007;16:271–82.
[16] Kubitza D, Becka M, Wensing G, et al. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939—an oral, direct Factor Xa inhibitor--after multiple dosing in healthy male subjects. Eur J Clin Pharmacol. 2005;61:873–80.
[17] Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:188S–203S.
[18] Ansell J, Hirsh J, Poller L, et al. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:204S–33S.
[19] Jun W, Wensheng Z, Xiaorui PEI, et al. Clinical study on the treatment of lower limb deep vein thrombosis with Danshen Chuanxiongzin injection combined with rivaroxaban. Modern Drugs Clin. 2018;33:3335–9.
[20] Li W, Zhang Y, Gu S. Clinical study on the treatment of lower limb venous thrombosis with ginkgodamol injection combined with rivaroxaban. Modern Drugs Clin. 2019;34:810–4.
[21] Ren Y, Huang YX, Yu X, et al. Clinical efficacy of rivaroxaban in combination with Yiqi antithrombotic pill in the treatment of lower limb deep vein thrombosis and its effect on coagulation function. Sichuan Med. 2020;41:1001–6.
[22] Yu ZH, Su BY, Tang P, et al. Efficacy of Danhong injection combined with rivaroxaban in the treatment of 35 cases of lower limb deep vein thrombosis. Huaxia Med. 2014;27:73–6.
[23] Yang AN, Wenge C, Jun WU, et al. Clinical study on the treatment of lower limb deep vein thrombosis with Qilisan acupressure combined with rivaroxaban under combined lumbar and rigid anesthesia. Jilin Chin Med. 2020;40:1372–5.
[24] Liu S, Yun W, Song H. Clinical efficacy of xiaoshuan Tongluo ointment combined with rivaroxaban in the treatment of stroke complicated with lower limb venous thrombosis. Clin Med Res Pract. 2020;5:111–2.
[25] Li Mingxia LY. Chinese medicine combined with rivaroxaban in the treatment of 75 cases of lower extremity venous thrombosis after gynecologic tumor. J Shaanxi Univ Tradit Chin Med. 2019;42:146–9.
[26] Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
[27] Jun Z. A method for activating blood circulation prevention and treatment of lower extremity deep vein thrombosis after hip arthroplasty in the retrospective study (a master's degree thesis, Hunan University of Chinese medicine). 2014. Available at: https://kns.cnki.net/KCMS/detail/detail.aspx?dbname=CMFD201 402&filename=1014241253.nh.
[28] Chen C, Tang Q, Zhang W, et al. Combination of traditional chinese medicine and low-molecular-weight heparin prevents deep vein thrombosis after surgery: a meta-analysis. Clin Appl Thromb Hemost. 2019;25:1076029619890411.
[29] Liu Q, Zhou SQ, Peng YP. Efficacy of Qing Ying cool blood and blood stasis soup combined with Rivaroxaban in the treatment of acute stage lower limb deep vein thrombosis. Shaanxi Tradit Chin Med. 2017;38:1745–6.
[30] Yanjie T, Pei C, Hua F, et al. Effects of ginkgodamol injection on lipid peroxidation in salivary gland tissues of diabetic rats. Chin J Clin Health Care. 2011;14:275–7.
[31] Tan P, Hao Y, Ding SJ, et al. Mechanism of platelet anti-aggregation with Ginkgo Biloba Extract. Chin J Neuromed. 2011;10:260–3.
[32] Cao J, Xia D, Wang W, et al. Clinical observation of maitongsan external application combined with rivaroxaban in the treatment of lower extremity deep vein thrombosis in patients with malignant tumor. Hebei Tradit Chin Med. 2020;42:230–4.
[33] Huo J, Huang Z, He Y. Effect of Buyang Huanwu Decoction and Simiao SAN on d-dimer and hypersensitive C-reactive protein in acute peripheral deep venous thrombosis of left lower extremity. Chinese Med Rev. 2019;16:128–31.
[34] Fung FY, Linn YC. Developing traditional Chinese medicine in the era of evidence-based medicine: current evidences and challenges. Evid Based Complement Alternat Med. 2015;2015:425037.