Combination of Traditional Chinese Medicine and Low-Molecular-Weight Heparin Prevenst Deep Vein Thrombosis After Surgery: A Meta-Analysis

Chu Chen, MD1,2,*, Qing Tang, BS3,*, Wenjuan Zhang, PhD2,*, Huijun Yuan, MM1, Ying Huai, PhD2, Kai Jiang, MD1, Yilun Wu, MB1, and Heping Zhao, MB1

Abstract
At present, there is no consistent understanding of the effect of traditional Chinese medicine (TCM) prescription in the prevention of the deep vein thrombosis (DVT), though TCM has been widely used in China. To evaluate the efficacy of TCM prescription combined with low-molecular-weight heparin (LMWH) for preventing DVT after major orthopedics surgery. All the retrieved articles were evaluated using specific inclusion and exclusion criteria. Then, data were extracted and evaluated for inclusion in a randomized controlled trial. In this study, variables included relative risk (RR), mean difference (MD), and their corresponding 95% confidence intervals (95% CIs). Overall, 16 articles were included with 1538 patients, 768 in the combination group (combination of TCM prescription and LMWH) and 770 in the LMWH group. The results indicated that in the combination group, the incidence of DVT (RR: 0.34, 95% CI: 0.23-0.50, \( P < .00001 \)) and D-dimer levels (standardized mean difference: \( -1.19, 95\% \) CI: \( -2.13 \) to \( -0.25, P = .0001 \)) was significantly lower than that in the LMWH group. Furthermore, the combination treatment obviously decreased the concentration of fibrinogen (MD: \( -1.19, 95\% \) CI: \( -2.13 \) to \( -0.25, P = .01 \)). The combination of TCM prescription and LMWH could significantly reduce the incidence of DVT, suggesting that it may be a more effective prophylaxis measure for DVT after major orthopedics surgery.

Keywords
deep vein thrombosis, low-molecular-weight heparin, traditional Chinese medicine, orthopedics major operation, meta-analysis

Date received: 1 August 2019; revised: 25 October 2019; accepted: 28 October 2019.

Introduction
Deep vein thrombosis (DVT) is one of the most common complications of patients with major orthopedics surgery, which mainly occurs in the lower limbs.1 Several patients with DVT may develop pulmonary embolism (PE), which might even lead to death.2 In the absence of any preventive measures, the incidence of DVT after surgery could reach up to 40% to 60%, the incidence of PE up to 20%, and the fatal PE up to 0.1% to 2%.3 Emerging evidence has shown that drug prevention is one of the most effective measures to reduce the risk of lower extremity DVT.4 For decades, the most widely used anticoagulants included warfarin, the heparin, low-molecular-weight heparin (LMWH), aspirin and novel oral anticoagulants (NOACs) in patients after major orthopedics surgery. Its purpose is to reduce the activity of plasma coagulation factor or the

Corresponding Authors:
Yilun Wu and Heping Zhao, Honghui Hospital, Xi’an JiaoTong University College of Medicine, Xi’an, Shaanxi 710054, China.
Emails: 381517535@qq.com; redcrossjyk@163.com

1 Honghui Hospital, Xi’an JiaoTong University College of Medicine, Xi’an, Shaanxi, China
2 Lab for Bone Metabolism, Key Lab for Space Biosciences and Biotechnology, Research Center for Special Medicine and Health Systems Engineering, NPU-UAB Joint Laboratory for Bone Metabolism, School of Life Sciences, Northwestern Polytechnical University, Xi’an, China
3 Tumor Stem Cell Research Institute, Dalian Medical University, Dalian, Liaoning, China
4 The first three authors contributed equally for this work.

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
activation of tissue plasma factor, so as to reduce the coagulation of blood, in order to prevent the formation of thrombus or the development of tissue thrombus. Although warfarin and heparin are used in the prevention of blood clotting, there are still some side effects, such as unusual bleeding, thrombocytopenia, and so on.6,7 Besides, in most cases, heparin requires continuous administration through intravenous injection and regular monitoring of activated partial thromboplastin time (APTT) levels to regulate the dosage. The pharmacological function of aspirin is mainly applied to prevent arterial thrombosis rather than to prevent venous thrombosis.7 The NOACs have the better safety and efficacy, but are expensive for long-term use. Low-molecular-weight heparin was relatively better, because it possesses good anticoagulant effect, few side effect, and usage convenience.

Notably, previous studies have already reported that traditional Chinese medicine (TCM) possess favorable curative efficacy in DVT. In fact, TCM have been used for the prevention of thrombosis for thousands of years in China. Traditional Chinese medicine not only exhibit good anticoagulation and anti-inflammation effects, but also benefit to improve circulation.8 Moreover, independent clinical studies have found that the combination of TCM prescription and LMWH is more effective in reducing the incidence of DVT. Due to the complicated prescription of TCM and the limited application in East Asia, there was still controversy to assess whether TCM could reduce the incidence of DVT.

Here, we aim to evaluate the efficacy of TCM prescription combined with LMWH for DVT prevention in patients with major orthopedics operation based on a meta-analysis of the data from the selected literature.

**Materials and Methods**

**Literature Search**

We searched electronic scientific literature databases like PubMed, Web of knowledge, the Chinese National Knowledge Infrastructure Database, the VIP Database, the Chinese Biomedical Database, and the Wan fang Database from January 2000 to January 2019. A combination of key words and free words were used to retrieve relevant research articles. The following key words were used: (“traditional Chinese and western medicine” or “traditional Chinese medicine” or “Chinese herb”) in combination with (“low molecular weight heparin” or “LMWH”) and (“deep venous thrombosis” or “DVT”) and (“orthopedics major operation”).

**Selection Criteria**

The article selection was based on the following inclusion criteria: (1) study design: randomized controlled trials (RCTs); (2) treatments: patients in the combination group had received TCM prescription and LMWH treatment, while those in the control group only had taken LMWH; (3) study subject: orthopedics major operation (total hip arthroplasty [THA], total knee arthroplasty [TKA], or hip fractures surgery); (4) relevant to the prevention of DVT after orthopedics major surgery; and (5) only included English and Chinese articles. Exclusion criteria include: (1) preoperative thrombosis; (2) literature lack of data integrity; (3) non-RCTs; (4) repeated publications; and (5) meeting reports, system evaluation, or summary articles.

**Data Extraction and Quality Assessment**

The data were extracted from all the included studies and consisted of 2 parts: basic information and main outcomes. Basic information included the author name, the intervention methods of combination and control groups, the sample size, and the operation type. Clinical outcomes included the incidence of DVT, the levels of d-dimer (D-D), prothrombin time (PT), APTT, and fibrinogen (FIB) concentration (Table 1).

The RCT assessment was conducted based on the Cochrane risk-assessment tool,25 which includes 6 domains: random allocation, allocation concealment, blind method, loss of outcome data, selection of outcome reporting, and other bias parameters. The assessment included a judgment assignment of “yes,” “no,” or “unclear” to each domain to designate a low, high, or unclear risk of bias, respectively.26 Publication bias assessment was performed with the use of the Review Manager 5.3. All the studies were screened by 2 investigators independently to determine whether they conform to the inclusion and exclusion criteria, and any disagreements were resolved through discussion or settled by a third review.

**Statistical Analysis**

All statistical data were analyzed on the Review Manager version 5.3 software (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen). Chi-square and I^2 tests were used to assess the heterogeneity of the clinical trial data and to decide the appropriate analysis model (fixed-effect model or random-effect model). When the chi-square test P value was ≤.05 and the I^2 tests value was >50%, the heterogeneity was defined as acceptable and the data were assessed by the random-effects model. Conversely, if the chi-square test P value was >.05 and the I^2 tests value was ≤50%, the data were defined as homogeneous and was assessed by the fixed-effects model. The continuous variables are expressed as the mean ± standard deviation and were assessed by the mean difference (MD). The categorical data are presented as percentages and were analyzed to calculate the relative risk (RR) or odds ratio. The risk of DVT was estimated by the RR and 95% confidence interval (95% CI). The MD along with 95% CI was used to evaluate the APTT, PT, and FIB. Because of the large difference in the mean of D-D levels, the standardized MD (SMD) was chosen to assess the combined effect quantity. Publication bias was evaluated by funnel plots.

**Results**

**Literature Search and Study Characteristics**

The details of the search strategy are shown in Figure 1. According to the search strategy and inclusion criteria, 428
articles were identified through the initial search, of which 16 RCTs comprising of 1538 patients (a total of 768 participants who received TCM prescription and LMWH; 770 participants who only received LMWH) were included in our meta-analysis. The Cochrane Collaboration tool was used to evaluate the quality of the eligible studies. As a result, 16 researches which reported the incidence of DVT after major orthopedics operation were included. The outcomes consist of APTT (14 RCTs, Table 2), PT (14 RCTs, Table 3), D-D (12 RCTs, Table 4), and FIB (8 RCTs, Table 5), respectively.

**Synopsis of Results**

**The incidence of DVT.** A total of 1538 patients (combination group = 768, control group = 770) after major orthopedics operation were reported in the included studies. According to the statistics, 132 patients had DVT, and among them, 32 cases with DVT in the combination group, whereas 100 patients with DVT in the control group. Given that chi-square test $P$ value was >.05 ($P = 1.00$) and the $I^2$ test value was $\leq 50\%$ ($I^2 = 0\%$), the fixed-effect model was used to analyze the incidence of DVT. The pooled results showed that the incidence of DVT was significantly lower (RR: 0.34, 95% CI: 0.23-0.50) in the combination group compared to that in the control group. These results are shown in Figures 2 and 3.

**Coagulation tests.** Twelve studies that involved 1206 patients referred the D-D levels; 13 studies that included 1357 patients measured PT and APTT, and 7 trials that involved 739 patients measured FIB concentration. The random-effects model was used to analyze coagulation effects because of the high-data heterogeneity ($I^2 > 75\%$). The analysis results showed that the D-D and FIB levels were significantly lower in the combination group than that in the control group (D-D: SMD = $-1.19$, 95% CI: $-1.80$ to $-0.58$, $P = .0001$, $I^2 = 96\%$; Figure 4; FIB: MD = $-1.19$, 95% CI: $-2.13$ to $-0.25$, $P = .01$, $I^2 = 97\%$; Figure 5). However, there were no statistical differences in the APTT (MD: 2.17, 95% CI: $-1.09$ to 5.43, $P = .19$, $I^2 = 97\%$; Figure 6) and the PT (MD: 1.06, 95% CI: $-0.73$ to 2.85, $P = .25$, $I^2 = 99\%$; Figure 7) between the 2 groups.

**Discussion**

Deep vein thrombosis is a serious complication with high incidence and is one of the most important factors causing unexpected death after major orthopedic surgery. Some studies have shown that the prevalence of DVT in the hip after trauma

![Figure 1. Flow diagram of the literature search and selection process.](image-url)
was up to 11.1% to 32.8%, and the incidence of DVT after THA and TKA was 2.4% to 6.49% and 3.19%, respectively. The classical symptoms of DVT are principally pain, tenderness, and swelling of the affected part. Moreover, it may endanger the patient’s life if the thrombus gets detached (thrombus dissolution) and travels to the lungs where it could cause PE. Effective thromboprophylaxis including drug prevention and physical prevention is vital for patients undergoing major orthopedic surgery. At present, anticoagulants have been commonly used in clinical practice, such as warfarin, the heparin, LMWH, aspirin, and NOACs. Among them, LMWH is one of the most widely used anticoagulants due to the high efficiency.

Table 1. The Basic Characteristics of Included Studies.

| Study          | Surgical Type | Sample Size | DVT | Preventive Measures                                                                 | Sample Size | DVT | Preventive Measures                                                                 | Outcome Indicators |
|---------------|---------------|-------------|-----|--------------------------------------------------------------------------------------|-------------|-----|--------------------------------------------------------------------------------------|-------------------|
| Li W (2017)²⁹ | THA           | 33          | 1   | On the basis of the control group, Huoxue Tongluo plaster                             | 36          | 3   | Low-molecular-weight heparin calcium                                                  | APTT/PT/PLT/D-D   |
| Li X (2015)¹⁰ | HFS           | 30          | 2   | On the basis of the control group, Huoxue Tongluo recipe                             | 30          | 8   | Low-molecular-weight heparin calcium                                                  | APTT/PT/D-D/FIB/DVT |
| Sun Z (2017)¹¹ | THA           | 30          | 0   | On the basis of the control group, Huoxue Lingfang compound                          | 30          | 0   | Low-molecular-weight heparin calcium                                                  | APTT/PT/TT/FIB/DVT |
| Feng J (2014)¹²| HFS           | 22          | 0   | On the basis of the control group, Danshen Chuanqiong soup                          | 21          | 2   | Low-molecular-weight heparin calcium                                                  | D-D/DVT          |
| Han H (2015)¹³| HFS           | 42          | 2   | On the basis of the control group, complex blood soup with peach and red soup.      | 42          | 6   | Low-molecular-weight heparin calcium                                                  | APTT/PT/TT/FIB/D-D/DVT |
| Zheng J (2018)⁴| HFS           | 70          | 2   | On the basis of the control group, Huoxue Tongmai recipe                             | 70          | 9   | Low-molecular-weight heparin calcium                                                  | APTT/PT/FIB/D-D   |
| Wang X (2017)¹⁵| HFS           | 68          | 2   | On the basis of the control group, Xiao Shuan soup                                  | 68          | 9   | Low-molecular-weight heparin calcium                                                  | DVT/D-D          |
| Tu Z (2015)¹⁶ | THR           | 48          | 2   | On the basis of the control group, traditional Chinese medicine                     | 52          | 9   | Low-molecular-weight heparin calcium                                                  | APTT/PT/D-D/DVT   |
| Chen G (2015)¹⁷| THR           | 56          | 7   | On the basis of the control group, Yiqi huoxue Tongmai soup                        | 56          | 15  | Low-molecular-weight heparin calcium                                                  | APTT/PT/DVT      |
| Tan L (2013)¹⁸| THR           | 102         | 3   | On the basis of the control group, Danggui Huoxue liquid                             | 104         | 7   | Low-molecular-weight heparin calcium                                                  | APTT/PT/FIB/DVT   |
| Sun Q (2011)¹⁹| HFS           | 31          | 2   | On the basis of the control group, Ginkgo Bilobate injection                        | 31          | 5   | Low-molecular-weight heparin calcium                                                  | APTT/PT/PLT/DVT   |
| Zheng H (2017)²⁰| HFS/THR      | 71          | 0   | On the basis of the control group                                                  | 75          | 2   | Low-molecular-weight heparin calcium                                                  | DVT/D-D/PT       |
| Lou H (2017)²¹| HFS/THA       | 37          | 2   | On the basis of the control group, Yiqi Tongmai recipe                             | 36          | 5   | Low-molecular-weight heparin calcium                                                  | DVT/APTT/PT/FIB/TT/D-D |
| Chen J (2017)²²| THA           | 52          | 4   | On the basis of the control group, Huoxue Fuyuan soup                             | 60          | 9   | Low-molecular-weight heparin sodium                                                   | DVT/APTT/PT/FIB   |
| Li C (2015)²³ | TKA           | 61          | 3   | On the basis of the control group, Yiqi Huoxue Tongluo soup                       | 55          | 9   | Low-molecular-weight heparin calcium                                                  | DVT/APTT/PT/FIB   |
| Zhang J (2014)²⁴| THA           | 20          | 0   | On the basis of the control group, Honghua Huangsesu                               | 20          | 2   | Low-molecular-weight heparin calcium                                                  | DVT/APTT/PT/PLI   |

Abbreviations: APTT, activated partial thromboplastin time; D-D, o-dimer; DVT, deep vein thrombosis; FIB, fibrinogen; HFS, hip fractures surgery; PT, prothrombin time; THA, total hip arthroplasty; TKA, total knee arthroplasty; THR, Total Hip Replacement operation; PLT, Platelets; TT, thrombin time.


Table 2. The Comparison of APTT (s) Between 2 Groups.

| Study   | Combination Group |                  | Control Group |                  |
|---------|-------------------|------------------|---------------|------------------|
|         | APTT (BD) n       | APTT (AD)        | APTT (BD) n   | APTT (AD)        |
| Li W    | 28.93 ± 2.84      | 30               | 32.39 ± 4.27  | 30               |
| Li X    | 21.99 ± 3.29      | 30               | 31.71 ± 5.76  | 30               |
| Sun Z   | 22.39 ± 2.35      | 30               | 19.41 ± 2.34  | 30               |
| Han H   | 39.27 ± 5.31      | 42               | 41.68 ± 5.42  | 42               |
| Zheng J | 36.90 ± 2.10      | 70               | 38.30 ± 2.10  | 70               |
| Tu Z    | 31.82 ± 5.57      | 48               | 30.82 ± 5.69  | 52               |
| Chen G  | 22.41 ± 2.62      | 56               | 34.57 ± 2.42  | 56               |
| Tan L   | 24.30 ± 1.90      | 102              | 38.40 ± 5.80  | 104              |
| Sun Q   | 30.48 ± 1.56      | 31               | 35.69 ± 5.96  | 31               |
| Lou H   | 42.60 ± 3.20      | 37               | 31.30 ± 3.40  | 36               |
| Chen J  | 30.57 ± 2.60      | 49               | 32.77 ± 2.58  | 49               |
| Li C    | 35.80 ± 7.22      | 61               | 34.49 ± 6.43  | 55               |
| Zhang J | 28.16 ± 2.89      | 20               | 35.69 ± 5.96  | 20               |

Abbreviation: APTT, activated partial thromboplastin time; BD, before drug; AD, after drug.

Table 3. The Comparison of PT (s) Between 2 Groups.

| Study   | Combination Group |                  | Control Group |                  |
|---------|-------------------|------------------|---------------|------------------|
|         | PT (BD) n         | PT (AD)          | PT (BD) n     | PT (AD)          |
| Li W    | 12.69 ± 0.61      | 30               | 12.71 ± 0.61  | 30               |
| Li X    | 10.61 ± 1.87      | 30               | 12.99 ± 0.72  | 30               |
| Sun Z   | 13.61 ± 1.43      | 30               | 10.72 ± 1.71  | 30               |
| Han H   | 12.85 ± 2.32      | 42               | 14.67 ± 2.83  | 42               |
| Zheng J | 12.20 ± 2.10      | 70               | 14.30 ± 2.10  | 70               |
| Tu Z    | 14.15 ± 1.32      | 48               | 14.04 ± 1.09  | 52               |
| Chen G  | 10.57 ± 0.42      | 56               | 18.59 ± 0.33  | 56               |
| Tan L   | 10.90 ± 1.20      | 102              | 17.00 ± 4.30  | 104              |
| Sun Q   | 11.48 ± 2.26      | 31               | 12.48 ± 1.75  | 31               |
| Zheng H | 11.70 ± 2.21      | 69               | 11.80 ± 1.67  | 70               |
| Lou H   | 17.50 ± 4.20      | 37               | 11.60 ± 3.00  | 36               |
| Chen J  | 11.40 ± 1.37      | 49               | 10.50 ± 1.33  | 49               |
| Li C    | 14.23 ± 1.89      | 61               | 14.01 ± 1.72  | 55               |
| Zhang J | 9.91 ± 4.46       | 20               | 16.63 ± 2.79  | 20               |

Abbreviation: PT, prothrombin time.

Table 4. The Comparison of D-D (μg/L) Between 2 Groups.

| Study   | Combination Group |                  | Control Group |                  |
|---------|-------------------|------------------|---------------|------------------|
|         | D-D (BD) n        | D-D (AD)         | D-D (BD) n    | D-D (AD)         |
| Li W    | 0.35 ± 0.10       | 30               | 0.98 ± 0.55   | 30               |
| Li X    | 1.54 ± 1.00       | 30               | 0.99 ± 0.51   | 30               |
| Sun Z   | 0.21 ± 0.16       | 30               | 0.42 ± 0.28   | 30               |
| Feng J  | 0.52 ± 0.03       | 22               | 0.47 ± 0.02   | 21               |
| Han H   | 4.80 ± 0.99       | 42               | 0.20 ± 0.50   | 42               |
| Zheng J | 0.37 ± 0.13       | 70               | 0.63 ± 0.11   | 70               |
| Wang X  | 8.97 ± 3.06       | 68               | 7.28 ± 3.83   | 68               |
| Tu Z    | 0.17 ± 0.16       | 48               | 0.08 ± 0.09   | 52               |
| Tan L   | 3.60 ± 0.10       | 102              | 1.60 ± 4.40   | 104              |
| Zheng H | 75.2 ± 5.67       | 69               | 73.6 ± 7.42   | 70               |
| Lou H   | 1.60 ± 0.40       | 37               | 74.90 ± 8.21  | 36               |
| Chen J  | 0.72 ± 0.26       | 49               | 0.40 ± 0.12   | 49               |

Abbreviation: D-D, d-dimer.
and low cost. However, the defect of LMWH lies in the need for subcutaneous injection, which might lead to subcutaneous nodules. As a side effect, LMWH has a very small probability of causing ecchymosis, mild hematoma, and necrosis at the injection site. Once such symptoms occur, the use of the drug will be stopped and would not be bright into clinical studies.

Accumulating evidences indicated that TCM possess unique advantages in the prevention of DVT, which have been successfully applied to patients with DVT. Traditional Chinese medicine prescription not only possess good efficacy of swelling reduction and blood stasis removal, but also promote blood circulation to remove obstruction in the channels of patients. Moreover, TCM could also protect vascular endothelin through multitarget regulation. In fact, TCM hold the supplementing Qi and activating blood circulation, which is considered the main

Table 5. The Comparison of FIB (g/L) Between 2 Groups.

| Study          | Combination Group | Control Group |
|----------------|-------------------|---------------|
|                | FIB (BD)          | n             | FIB (AD) | FIB (BD) | n | FIB (AD) |
| Li X (2015)    | 3.99 ± 1.08       | 30            | 3.13 ± 0.54 | 3.72 ± 0.85 | 30 | 3.21 ± 0.72 |
| Sun Z (2017)   | 3.41 ± 0.68       | 30            | 3.12 ± 1.21 | 3.53 ± 0.71 | 30 | 3.95 ± 0.94 |
| Han H (2015)   | 5.15 ± 1.81       | 42            | 3.82 ± 1.42 | 5.18 ± 1.76 | 42 | 4.16 ± 1.50 |
| Zheng J (2018) | 3.40 ± 0.30       | 70            | 4.20 ± 2.20 | 3.30 ± 0.70 | 70 | 5.50 ± 2.10 |
| Tan L (2013)   | 4.80 ± 0.70       | 102           | 3.80 ± 4.20 | 4.20 ± 0.40 | 104 | 10.30 ± 2.60 |
| Lou H (2017)   | 2.40 ± 0.50       | 37            | 3.60 ± 0.30 | 2.40 ± 0.50 | 36 | 3.20 ± 0.40 |
| Chen J (2017)  | 3.09 ± 0.23       | 49            | 3.39 ± 0.56 | 3.10 ± 0.36 | 49 | 4.92 ± 0.44 |
| Li C (2015)    | 4.94 ± 1.2        | 61            | 4.44 ± 1.02 | 4.91 ± 1.30 | 55 | 4.72 ± 1.15 |

Abbreviation: FIB, fibrinogen.

Figure 2. Forest plot that shows the comparison of the incidence of DVT between the combination group and the control group.

Figure 3. Funnel plot that shows the comparison of the incidence of DVT.
Figure 4. Forest plot that shows the comparison of the D-D between the combination group and the control group.

Figure 5. Forest plot that shows the comparison of the FIB between the combination group and the control group.

Figure 6. Forest plot that shows the comparison of the APTT between the combination group and the control group.
strategy for the prevention and treatment of DVT after opera-
tion. The most frequently used prescription is Buyang Huanwu
decoction, which is composed of 7 medicines: Shenghuangqi
(Astragalus membranaceus [Fisch] Bge), Guwei (Angelica
sinensis [Oliv.] Diels), Chishao (Paeonia veitchii Lynch),
Dilong (Pheretima vulgaris Chen), Chuangxiong (Ligusticum
chuanxiong Hort), Honghua (Carthamus tinctorius L), and
Taoren (Prunus persica [L] Batsch).33,34 Recent studies have
discovered that Buyang Huanwu decoction could increase the
proliferation of endogenous endothelial progenitor cells and
the expression of serum nitric oxide levels, endothelin-1, and
γ-interferon, which could improve abnormal contraction of
blood vessels, protect the vascular endothelium, and inhibit
platelet adhesion, thereby inhibiting thrombosis.35 In included
RCTs, the most common herbs for DVT prevention include
Honghua, Danshen (Salvia miltiorrhiza Bge), Danggui (Angel-
ica sinensis [Oliv] Diels), Taoren, Chishao, Shengdihuang,
Chuanxiong, and so on. Among them, Honghua and Danggui
exhibit good effects in activating blood flow and eliminating
blood stasis.36 Danshen could prevent thrombosis by expand-
ing the peripheral vessels and increasing the activity of plas-
min.37 Chuanxiong is used for preventing thrombosis by
reducing platelet activity and inhibiting aggregation of plate-
lets.38 Taoren can reduce blood viscosity and inhibit micro-
thrombus formation.39 In summary, these herbal medicines
could be used to improve the clinical symptoms of DVT for-
mation in the lower extremities.

This meta-analysis included 16 RCTs which assessed the
efficacy of TCM prescription combined with LMWH for
DVT prevention after major orthopedics operation. Our
results indicated that TCM prescription combined with
LMWH is more effective for the prevention of DVT; the
incidence rate of DVT in the combination group was signif-
ificantly lower ($P < .01$) than the control group. In addition,
there were significant differences in the D-D and FIB levels
between the combination group and control group ($P \leq .01$).
D-Dimer, as a plasma marker of endogenous fibrinolysis, is
sensitive and helpful in the diagnosis of DVT. Dynamic mon-
toring of the plasma D-D could be used for the evaluation of
the clinical effect of anticoagulant therapy and secondary
fibrinolysis and might act as an indicator for the prediction
of thrombosis.40,41 Positive detection of D-D could not predict
the formation of disease; on the contrary, D-D negative could
basically exclude DVT. The concentration of FIB in the com-
bined TCM and LMWH group was significantly lower than
that in the LMWH group ($P < 0.01$). Fibrinogen is a
coagulation-producing protein synthesized by the liver. The
increase of FIB indicates that the blood is in a state of high
coagulation, which could slow down the blood speed and
increase the blood viscosity, therefore prone to thrombosis.
However, there was no statistical difference in PT and APTT
between the 2 groups ($P > .05$); the values were still in the
reference range.

We acknowledge some potential limitations in this study
that should be considered. First, in spite of many databases at
home and abroad have been systematically searched, the num-
ber of literatures that can be included and the sample size in the
study are small, and the statistical efficiency may be insuffi-
cient; Second, the differences of TCM prescriptions used in
each study and the course of treatment were caused by different
factors, but the number of studies included in each index was
relatively small. This study failed to further explore the source
of heterogeneity and parallel subgroup analysis, nor did it carry
out publication bias test; Third, none of the studies reported the
number of adverse reactions in the course of treatment. There-
fore, we have no ability to evaluate the safety of integrated
TCM and LMWH therapy.

This meta-analysis assessed the efficacy of the combination
of TCM prescription and LMWH on DVT prevention after
lower extremity orthopedic surgery. In conclusion, we

Figure 7. Forest plot that shows the comparison of the PT between the combination group and the control group.
observed that the combination of TCM prescription and LMWH could significantly reduce the incidence of DVT, suggesting that it may be a more effective prophylaxis measure for DVT after major orthopedics surgery.

Traditional Chinese medicine has a history of thousands of years in China and has formed a set of its own medical theory system. However, with the decline of modern China, the research of TCM and TCM theory also lags behind. With the exception of Chinese medicine doctors, most doctors are skeptical about the use of TCM. In the choice of anticoagulant drugs for the prevention of DVT, Chinese medicine doctors have developed some drugs using their own theoretical system. Although some achievements have been made in clinical application, these studies are scattered and independent. The lack of systematic research limits the use and development of anticoagulant drugs of TCM. Our research is to promote the development of anticoagulant drugs of TCM, the scattered research will be systematically analyzed to explain the functions and characteristics of anticoagulant drugs of TCM.

Authors’ Note

Chu Chen, and Qing Tang involved in data curation; Chu Chen, Qing Tang, and Wenjuan Zhang involved in formal analysis; Wenjuan Zhang involved in funding acquisition; Ying Huai, Huijun Yuan, and Kai Jiang performed investigation; Qing Tang and Chu Chen performed methodology; Qing Tan performed Software; Qing Tang contributed to writing original draft; Chu Chen, Wenjuan Zhang, Heping Zhao, and Yilun Wu involved in writing review and editing. All the authors proofread and approved the final manuscript.

Acknowledgments

All the authors of the manuscript are immensely grateful to their respective universities and institutes for their technical assistance and valuable support in the completion of this research project.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Fund of the Fundamental Research Funds for the Central Universities (No. 3102017QJD050) and China’s Postdoctoral Science Fund (No. 2017M623249).

ORCID iD

Qing Tang https://orcid.org/0000-0003-6251-2526

References

1. Decker S, Weaver MJ. Deep venous thrombosis following different isolated lower extremity fractures: what is known about prevalences, locations, risk factors and prophylaxis? Eur J Trauma Emerg S. 2013;39(6):591-598.
2. Huang L, Li J, Jiang Y. Association between hypertension and deep vein thrombosis after orthopedic surgery: a meta-analysis. Eur J Med Res 2016;21(1):1-7.
3. Bates SM, Greer IA, Pabinger I, Sosaer S, Hirsh J. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American college of chest physicians evidence-based clinical practice guidelines (8th edition). Chest. 2008;133(6):844S-866S.
4. Tufano A, Coppola A, Cerceo A M, et al. Preventing postsurgical venous thromboembolism: pharmacological approaches. Thie Med Publish. 2011;37(03):252-266.
5. Khandelwal S, Areppally GM. Immune pathogenesis of heparin-induced thrombocytopenia. J Thromb Haemost. 2016;11(5):792-798.
6. Greinacher A, Selleng K, Warkentin TE. Autoimmune heparin-induced thrombocytopenia. J Thromb Haemost. 2017;15(11):2099.
7. Mekaj YH, Daci FT, Mekaj AY. New insights into the mechanisms of action of aspirin and its use in the prevention and treatment of arterial and venous thromboembolism. Ther Clin Risk Mana. 2015;11(default):1449-1456.
8. Lim JW, Chee SX, Wong WJ, He QL, Lau TC. Traditional Chinese medicine: herb-drug interactions with aspirin. Singap Med J. 2018;59(5):230-239.
9. Li WL, Li YY, Zhang HL, Wang HC, Liu YW. Clinical study of application of huoxue tongluo ointment combing low-molecular-weight heparin calcium injection in preventing deep venous thrombosis after total hip arthroplasty. Journal of Emergency in Traditional Chinese Medicine 2017;26(2):339-342.
10. Li XJ, Tang WZ. A clinical observation of tongmaihuoxue decoction with low molecular weight heparin calcium treating post hip surgery lower extremity deep vein thrombosis. J Emerg Trad Chin Med. 2015;24(2):227-230.
11. Sun Z, Zhang HJ, Fan KM. Clinical research of huoxue decocction combine with nadroparin calcium in preventing deep venous thrombosis of lower extremities after hip arthroplasty. Clin J Trad Chin Med. 2017;21(04):115-117.
12. Feng JH, Liu WC. Clinical Efficacy of prevention from lower limb deep venous thrombosis after peripheral hip fracture in the elderly treated with salvia milto-rhiza ligustrazine and low molecular heparin. World J Int Trad West Med. 2014, (8), 867-869.
13. Han HQ, Li AM, Chen J, Pu M. Therapeutic effect of integrated traditional Chinese and western medicine on prevention of deep vein thrombosis after hip replacement. Guid J Trad Chin Med Pharm. 2015;73(20):67-69.
14. Zhen JJ. Study on prevention of deep vein thrombosis after operation of hip surgery by guyi decoction and low molecular weight heparin. J Trad Chin Med. 2017;47(09):35-37.
15. Wang XL, Zan Q, Li XQ, et al. Clinical study on “Xieshuo Decoction” combined with low molecular weight heparin calcium in prevention of 68 cases of lower extremity deep vein thrombosis after hip fracture. Jian J Trad Chin Med. 2017;49(8):35-37.
16. Tu ZS, Bao HS, Feng ZQ, Qiu YG. Prevention of deep vein thrombosis by guyi decoction and low molecular weight heparin following total hip replacement. J Guang Univers Trad Chin Med. 2015;32(2):199-203.
17. Chen G, Qiang S, Deng T. Effect of Yiqi Huoxue tongluo decoction in the treatment of the deep vein thrombosis on the lower limb caused by artificial hip joint replacement. J Sichu Trad Chin Med. 2015;33(3):80-81.
18. Tan LM, Zou XJ, Xin XC, Liu DA. Angelica live blood combined with low molecular weight heparin calcium to prevent deep venous thrombosis of lower limbs after artificial hip joint replacement. Gai J Trad Chin Med Pharm. 2013;25(4):54-56.
19. Sun Q, Peng DF, Zhen JF. Clinical observation of Xiaoshuan decoction combined with low molecular weight heparin sodium in preventing deep venous thrombosis after the operation of intertrochanteric fracture. Hebei J Trad Chin Med. 2011;31(11):1463-1465.
20. Zheng H, Chen X, Zhang W, Orthopedics DO. Clinical observation of preventive action of blood-activating and detumescence recipe combined with low molecular weight heparin calcium on deep vein thrombosis of lower limbs after orthopaedics major operation. Hebei J Trad Chin Med. 2017;39(4):550-553.
21. Lou HK, Jin Y, Wang KT. Comparison of Yiqi Tongmai recipe and low molecular weight heparin calcium in preventing lower extremity deep vein thrombosis in hip surgery. Chin J Rural Med Pharm. 2017;24(19):27-28.
22. Chen J, Liu Y, Wang N, Huang Y, Yu Y, Wang Y. Clinical study of Xiaoshuan decoction combined with low molecular weight heparin sodium in preventing deep vein thrombosis after femoral shaft fracture. Hunan J Trad Chin Med. 2017;33(3):68-70.
23. Li CL, Li ZW. Effect of low molecular weight heparin combined with traditional Chinese medicine iontophoresis on prevention of deep venous thrombosis of lower extremity after knee joint replacement in the elderly. Chin J Gerontol. 2015;(13):3671-3673.
24. Zhang JQ. Clinical observation of safflower yellow pigment injection combined with low molecular weight heparin calcium in preventing deep venous thrombosis of lower limb after hip joint replacement. Hunan J Trad Chin Med. 2014;30(5):71-72.
25. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane collaboration’s tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
26. Huang HF, Tian JL, Yang XT, et al. Efficacy and safety of low-molecular-weight heparin after knee arthroscopy: a meta-analysis. PLoS One. 2018;13(6):e0197868.
27. Yamasaki K, Hoshino M, Omori K, et al. Prevalence and risk factors of deep vein thrombosis in patients undergoing lumbar spine surgery. J Orthop Sci. 2017;22(6):1021-1025.
28. Zhang BF, Wei X, Huang H, et al. Deep vein thrombosis in bilateral lower extremities after hip fracture: a retrospective study of 463 patients. Clin Interv Aging. 2018;13:681-689.
29. Elhassan B, Karabekmez F, Hsu CC, Steinmann S, Moran S. Outcome of local anconeus flap transfer to cover soft tissue defects over the posterior aspect of the elbow. J Shoulder Elbow Surg. 2011;20(5):807-812.
30. Rui Y, Wang D, Hu D, Huang L. Role of dalteparin sodium on the growth of cancer cells and tumor-associated angiogenesis in A549 human lung cancer cell line and grafted mouse model. J Cancer Res Ther. 2018;14(supplement):S985-S992.
31. Zhang HX, Ma HF, Yuan J. Combined effect of traditional Chinese medicine decoction and low-molecular-weight heparin calcium on the postoperative deep venous thrombosis in patients with lower limb fracture. World J Trad West Med. 2015;1(1):9-13.
32. Zhu S, Song Y, Chen X, Qian W. Traditional Chinese and western medicine for the prevention of deep venous thrombosis after lower extremity orthopedic surgery: a meta-analysis of randomized controlled trials. J Orthop Surg Res. 2018;13(1):79.
33. Yang WY, Pan JK, Liu J, Guo D, Lv R, Cao XW. Study on the rule of Chinese medicine for prevention and treatment of deep vein thrombosis after hip and knee joint replacement. Guid J Trad Chin Med Pharm. 2017;(21):25-27.
34. Yang K, Yang CM, Pang WS, Han J, Hu J. Anti-platelet aggregation of Buyang Huanwu decoction. Chin J Ethnomed Ethnopharm. 2013;22(1):42-42.
35. Huang X, Li YG, Kou GJ, Huang YH, Wang BH. Advances in research on anti-atherosclerosis mechanism of Buyang Huanwu decoction. Chin J Trad Chin Med Pharm. 2017;32(3):1187-1190.
36. Li Y, Wang N. Antithrombotic effects of Danggui, Honghua and potential drug interaction with clopidogrel. J Ethnopharmacol. 2010;128(3):623-628.
37. Feng J, Wang SC. Effect of Fufang Danshen Diwan to platelet aggregation function. Chin J Misdiagn. 2006;6(12):2261-2263.
38. Chen JJ, Zhuang YF. Progress of traditional Chinese medicine in prevention and treatment of deep venous thrombosis after total hip arthroplasty. Chin Med Herald. 2016;13(16):104-107.
39. Yi M, Xu JY, Hao EW, Deng JG. Antithrombotic mechanism of persicae semen extract in blood stasis rats. Chin J Exp Trad Med Form. 2016;(1):125-128.
40. Sudo A, Wada H, Nobori T, et al. Cut-off values of D-dimer and soluble fibrin for prediction of deep vein thrombosis after orthopaedic surgery. Int J Lab Hematol. 2009;31(5):572-576.
41. Wada H, Sakuragawa N. Are fibrin-related markers useful for the diagnosis of thrombosis? Semin Thromb Hemost. 2008;34(01):033-038.