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

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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: -1.80 to -0.58, $P = .0001$) 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

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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

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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.[5,6] 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 $\leq .05$ 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 $\leq$50%, the data were defined as homogeneous and was assessed by the fixed-effects model. The continuous variables are expressed as the mean $\pm$ 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

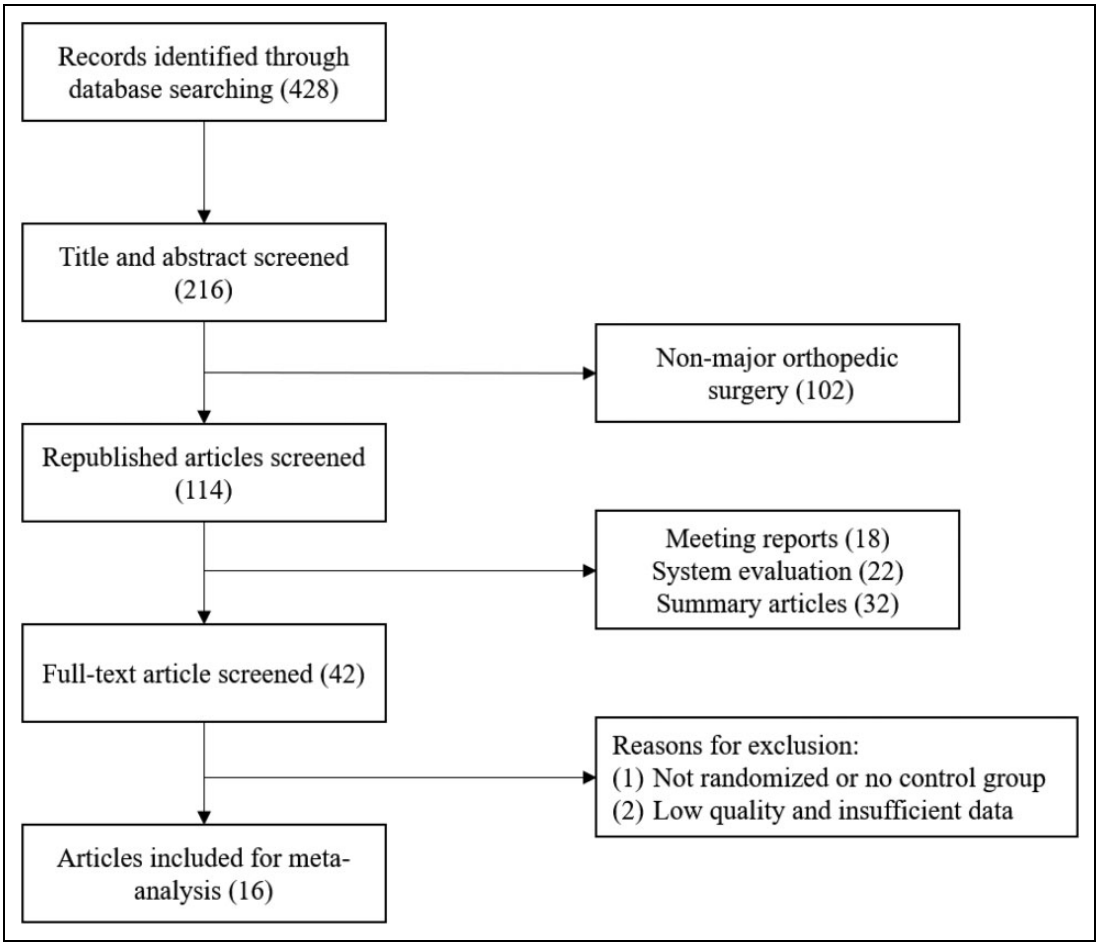

Figure 1. Flow diagram of the literature search and selection process.

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 ≤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.[27] Some studies have shown that the prevalence of DVT in the hip after trauma

Table 1. The Basic Characteristics of Included Studies.

		Combination Group			Control Group			
Study	Surgical Type	Sample Size	DVT	Preventive Measures	Sample Size	DVT	Preventive Measures	Outcome Indicators
Li W (2017)[9]	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/DVT
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/D-D/DVT
Feng J (2014)[12]	HFS	22	0	On the basis of the control group, Danshen Chuanqiong soup	21	2	Low-molecular-weight heparin	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)[14]	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/DVT
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	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/D-D
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 THA	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	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, D-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.

was up to 11.1% to 32.8%,[28] 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.[29] 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 2. The Comparison of APTT (s) Between 2 Groups.

	Combination Group			Control Group		
Study	APTT (BD)	n	APTT (AD)	APTT (BD)	n	APTT (AD)
Li W (2017)[9]	28.93 ± 2.84	30	32.39 ± 4.27	27.79 ± 3.77	30	29.96 ± 4.48
Li X (2015)[10]	21.99 ± 3.29	30	31.71 ± 5.76	21.09 ± 2.26	30	28.77 ± 4.51
Sun Z (2017)[11]	22.39 ± 2.35	30	19.41 ± 2.34	22.13 ± 2.13	30	18.13 ± 2.27
Han H (2015)[13]	39.27 ± 5.31	42	41.68 ± 5.42	40.05 ± 5.26	42	41.25 ± 5.39
Zheng J (2018)[14]	36.90 ± 2.10	70	38.30 ± 2.10	36.60 ± 2.30	70	37.50 ± 3.10
Tu Z (2015)[16]	31.82 ± 5.57	48	30.82 ± 5.69	32.41 ± 4.72	52	33.51 ± 5.42
Chen G (2015)[17]	22.41 ± 2.62	56	34.57 ± 2.42	22.39 ± 2.58	56	31.18 ± 2.43
Tan L (2013)[18]	24.30 ± 1.90	102	38.40 ± 5.80	23.60 ± 1.90	104	21.40 ± 3.20
Sun Q (2011)[19]	30.48 ± 1.56	31	35.69 ± 5.96	32.56 ± 4.86	31	30.48 ± 1.56
Lou H (2017)[21]	42.60 ± 3.20	37	31.30 ± 3.40	43.70 ± 4.00	36	35.50 ± 3.30
Chen J (2017)[22]	30.57 ± 2.60	49	32.77 ± 2.58	30.33 ± 2.60	49	36.90 ± 2.45
Li C (2015)[23]	35.80 ± 7.22	61	34.49 ± 6.43	35.69 ± 7.14	55	33.92 ± 6.05
Zhang J (2014)[24]	28.16 ± 2.89	20	35.69 ± 5.96	29.48 ± 0.96	20	30.48 ± 1.56

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

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

	Combination Group			Control Group		
Study	PT (BD)	n	PT (AD)	PT (BD)	n	PT (BD)
Li W (2017)[9]	12.69 ± 0.61	30	12.71 ± 0.61	12.92 ± 0.76	30	12.14 ± 0.85
Li X (2015)[10]	10.61 ± 1.87	30	12.99 ± 0.72	10.22 ± 1.64	30	12.07 ± 1.03
Sun Z (2017)[11]	13.61 ± 1.43	30	10.72 ± 1.71	13.53 ± 1.58	30	9.79 ± 1.60
Han H (2015)[13]	12.85 ± 2.32	42	14.67 ± 2.83	12.93 ± 2.57	42	13.28 ± 2.91
Zheng J (2018)[14]	12.20 ± 2.10	70	14.30 ± 2.10	11.50 ± 2.10	70	13.50 ± 3.10
Tu Z (2015)[16]	14.15 ± 1.32	48	14.04 ± 1.09	14.22 ± 1.29	52	14.73 ± 1.07
Chen G (2015)[17]	10.57 ± 0.42	56	18.59 ± 0.33	10.58 ± 0.43	56	13.46 ± 0.31
Tan L (2013)[18]	10.90 ± 1.20	102	17.00 ± 4.30	11.40 ± 1.10	104	10.40 ± 3.10
Sun Q (2011)[19]	11.48 ± 2.26	31	12.48 ± 1.75	11.76 ± 0.96	31	10.56 ± 1.19
Zheng H (2017)[20]	11.70 ± 2.21	69	11.80 ± 1.67	11.90 ± 1.34	70	11.80 ± 1.24
Lou H (2017)[21]	17.50 ± 4.20	37	11.60 ± 3.00	18.20 ± 4.90	36	14.40 ± 3.00
Chen J (2017)[22]	11.40 ± 1.37	49	10.50 ± 1.33	11.56 ± 1.58	49	13.73 ± 1.64
Li C (2015)[23]	14.23 ± 1.89	61	14.01 ± 1.72	14.21 ± 1.86	55	13.88 ± 1.64
Zhang J (2014)[24]	9.91 ± 4.46	20	16.63 ± 2.79	10.70 ± 0.63	20	13.40 ± 2.62

Abbreviation: PT, prothrombin time.

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

	Combination Group			Control Group		
Study	D-D (BD)	n	D-D (AD)	D-D (BD)	n	D-D (AD)
Li W (2017)[9]	0.35 ± 0.10	30	0.98 ± 0.55	0.98 ± 0.55	30	1.16 ± 0.40
Li X (2015)[10]	1.54 ± 1.00	30	0.99 ± 0.51	1.63 ± 0.77	30	1.20 ± 0.43
Sun Z (2017)[11]	0.21 ± 0.16	30	0.42 ± 0.28	0.24 ± 0.17	30	0.53 ± 0.24
Feng J (2014)[12]	0.52 ± 0.03	22	0.47 ± 0.02	0.53 ± 0.03	21	0.52 ± 0.03
Han H (2015)[13]	4.80 ± 0.99	42	0.20 ± 0.50	0.49 ± 0.99	42	3.40 ± 0.53
Zheng J (2018)[14]	0.37 ± 0.13	70	0.63 ± 0.11	0.36 ± 0.17	70	0.74 ± 0.12
Wang X (2017)[15]	8.97 ± 3.06	68	7.28 ± 3.83	8.65 ± 2.72	68	7.11 ± 4.33
Tu Z (2015)[16]	0.17 ± 0.16	48	0.18 ± 0.09	0.18 ± 0.11	52	0.22 ± 0.08
Tan L (2013)[18]	3.60 ± 0.10	102	1.60 ± 4.40	3.30 ± 0.40	104	9.40 ± 2.40
Zheng H (2017)[20]	75.2 ± 5.67	69	73.6 ± 7.42	0.50 ± 0.20	70	75.20 ± 7.63
Lou H (2017)[21]	1.60 ± 0.40	37	74.90 ± 8.21	1.70 ± 0.40	36	0.80 ± 0.30
Chen J (2017)[22]	0.72 ± 0.26	49	0.40 ± 0.12	0.63 ± 0.30	49	0.87 ± 0.12

Abbreviation: D-D, D-dimer.

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

	Combination Group			Control Group		
Study	FIB (BD)	n	FIB (AD)	FIB (BD)	n	FIB (AD)
Li X (2015)[10]	3.99 ± 1.08	30	3.13 ± 0.54	3.72 ± 0.85	30	3.21 ± 0.72
Sun Z (2017)[11]	3.41 ± 0.68	30	3.12 ± 1.21	3.53 ± 0.71	30	3.95 ± 0.94
Han H (2015)[13]	5.15 ± 1.81	42	3.82 ± 1.42	5.18 ± 1.76	42	4.16 ± 1.50
Zheng J (2018)[14]	3.40 ± 0.30	70	4.20 ± 2.20	3.30 ± 0.70	70	5.50 ± 2.10
Tan L (2013)[18]	4.80 ± 0.70	102	3.80 ± 4.20	4.20 ± 0.40	104	10.30 ± 2.60
Lou H (2017)[21]	2.40 ± 0.50	37	3.60 ± 0.30	2.40 ± 0.50	36	3.20 ± 0.40
Chen J (2017)[22]	3.09 ± 0.23	49	3.39 ± 0.56	3.10 ± 0.36	49	4.92 ± 0.44
Li C (2015)[23]	4.94 ± 1.2	61	4.44 ± 1.02	4.91 ± 1.30	55	4.72 ± 1.15

Abbreviation: FIB, fibrinogen.

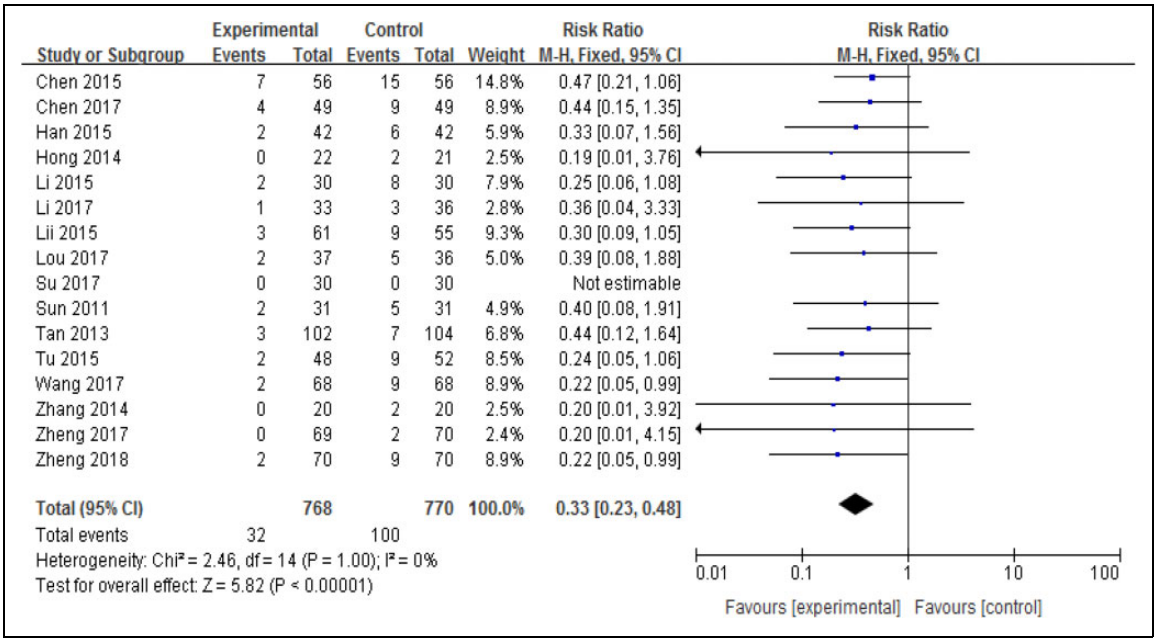

Figure 2. Forest plot that shows the comparison of the incidence of DVT between the combination group and the control group.

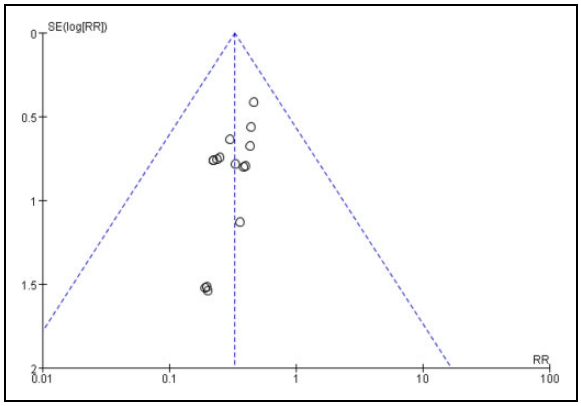

Figure 3. Funnel plot that shows the comparison of the incidence of DVT.

and low cost. However, the defect of LMWH lies in the need for subcutaneous injection, which might lead to subcutaneous nodules.[30] 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.[31] 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.[32] 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

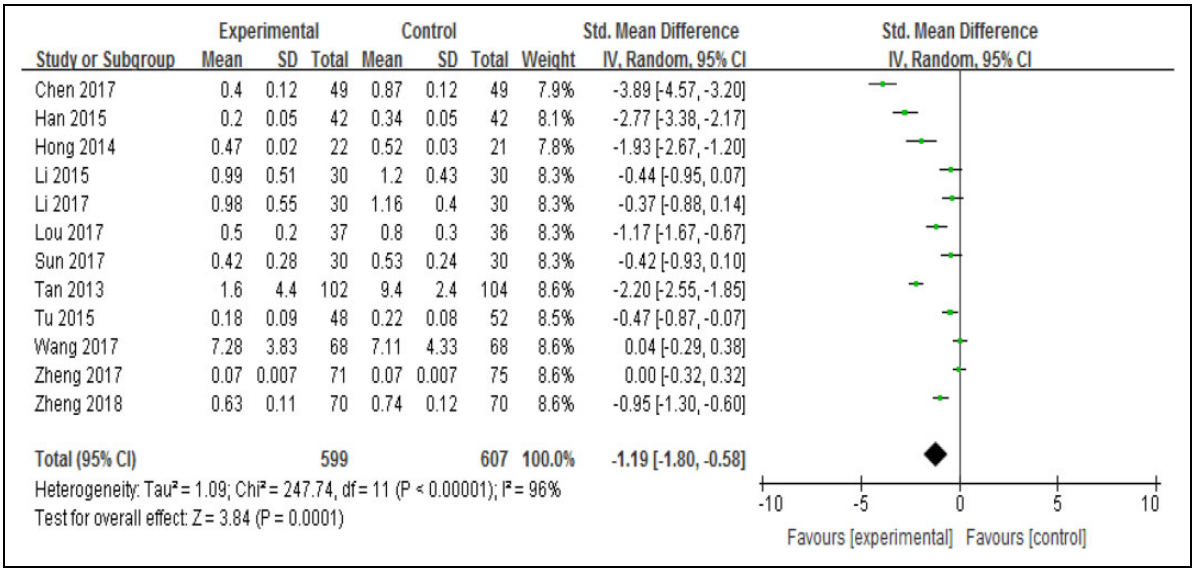

Figure 4. Forest plot that shows the comparison of the D-D between the combination group and the control group.

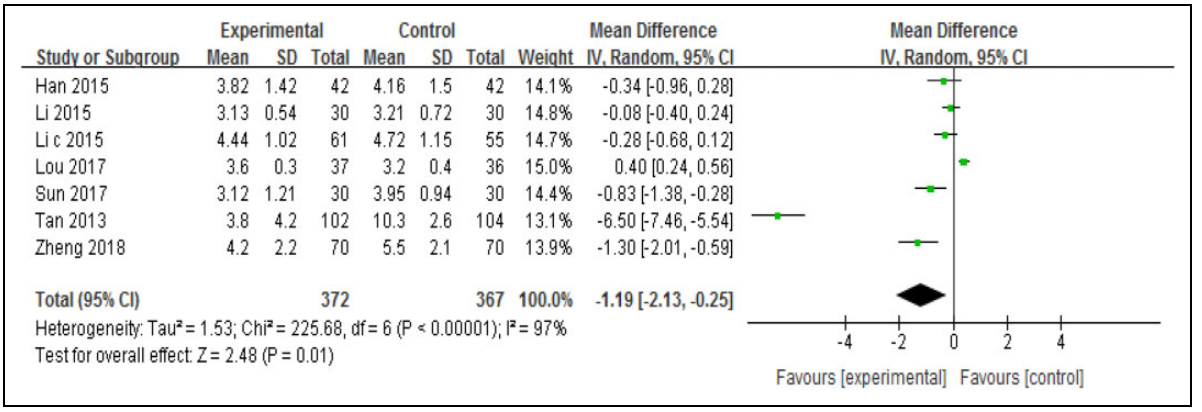

Figure 5. Forest plot that shows the comparison of the FIB between the combination group and the control group.

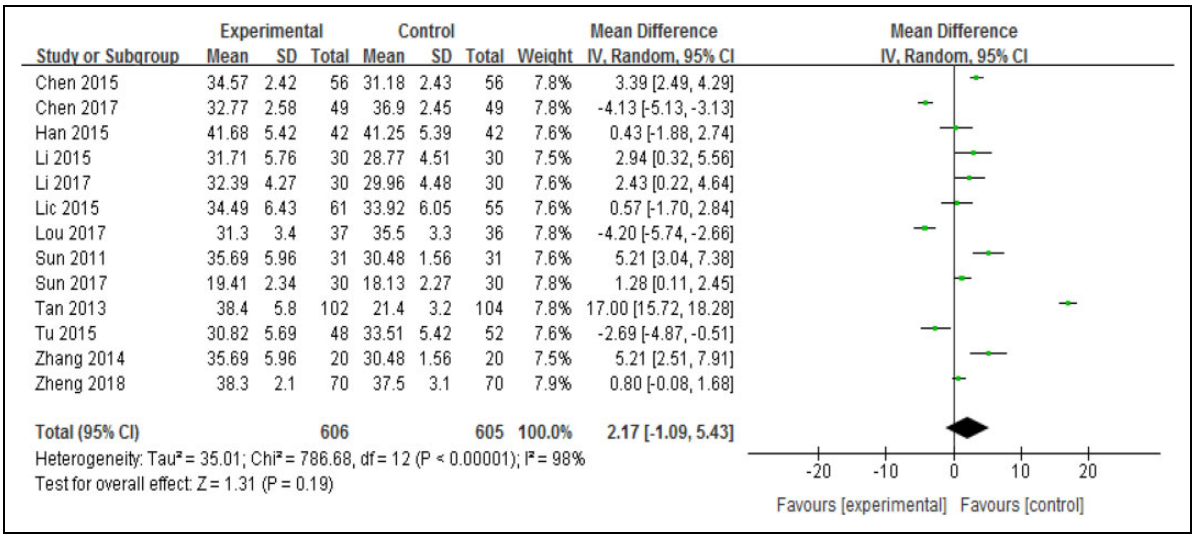

Figure 6. Forest plot that shows the comparison of the APTT between the combination group and the control group.

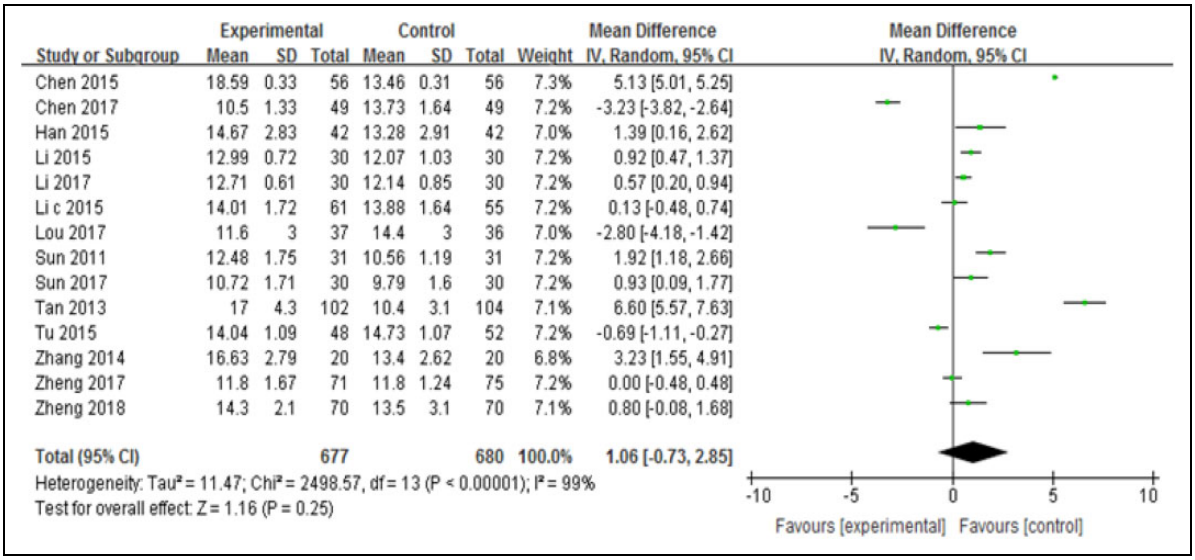

Figure 7. Forest plot that shows the comparison of the PT between the combination group and the control group.

strategy for the prevention and treatment of DVT after operation. The most frequently used prescription is Buyang Huanwu decoction, which is composed of 7 medicines: Shenghuangqi (*Astragalus membranaceus [Fisch]) Bge*), Guiwei (*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 (*Angelica 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 expanding the peripheral vessels and increasing the activity of plasmin.[37] Chuanxiong is used for preventing thrombosis by reducing platelet activity and inhibiting aggregation of platelets.[38] Taoren can reduce blood viscosity and inhibit microthrombus formation.[39] In summary, these herbal medicines could be used to improve the clinical symptoms of DVT formation 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 significantly 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 monitoring 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 combined 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 number of literatures that can be included and the sample size in the study are small, and the statistical efficiency may be insufficient; 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. Therefore, 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

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.

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