Am J Transl Res 2024;16(11):6626-6635
www.ajtr.org /ISSN:1943-8141/AJTR0156202

Original Article

Efficacy and safety of safflower yellow combined with low molecular weight heparin in preventing deep vein thrombosis after orthopedic surgery: a systematic review and meta-analysis

Qiuyu Li[1*], Lu Liu[1*], Wenjie Yin[2], Zhuo Zhu[2], Hong Xu[2]

[1]Department of Intensive Care Unit, Kunming Medical University Affiliated Yan'an Hospital, Kunming 650051, Yunnan, China; [2]Department of Pharmacy, Kunming Medical University Affiliated Yan'an Hospital, Kunming 650051, Yunnan, China. [*]Equal contributors and co-first authors.

Received February 28, 2024; Accepted June 7, 2024; Epub November 15, 2024; Published November 30, 2024

Abstract: Objective: This systematic review and meta-analysis aims to evaluate the efficacy and safety of safflower yellow (SY) combined with low molecular weight heparin (LMWH) in preventing deep vein thrombosis (DVT) after orthopedic surgery. Methods: We conducted a comprehensive investigation of PubMed, EMbase, Cochrane Library, CNKI, VIP, and Wanfang databases to identify randomized controlled trials (RCTs) from January 2000 to March 2024. These trials compared the efficacy of SY combined with LMWH versus LMWH alone in preventing post-surgical DVT. Primary outcomes were the incidence of DVT, activated partial thromboplastin time (APTT), and prothrombin time (PT). The methodological quality of included studies was assessed using the modified Jadad scale. The meta-analysis, conducted with using RevMan 5.3 and STATA, employed fixed or random-effects models depending on heterogeneity assessments. It calculated risk ratios (RR) for DVT incidence and mean differences for APTT/PT, while also evaluating robustness and publication bias. Significance thresholds were set at $P < 0.05$ and $P < 0.1$, respectively. Results: Our analysis included eight RCTs involving 624 patients. The meta-analysis revealed that the combination of SY and LMWH significantly reduced the incidence of DVT (RR: 0.29, 95% CI: 0.16-0.52) compared to LMWH alone, with no difference in adverse reaction rate. Additionally, the combination therapy demonstrated improved APTT and PT profiles. Conclusion: The combination of SY and LMWH is more effective than LMWH alone for preventing DVT post orthopedic surgery, offering a promising alternative for thromboprophylaxis in these patients.

Keywords: Safflower yellow, low molecular weight heparin, orthopedic surgery, deep vein thrombosis, meta-analysis

Introduction

Currently, surgical techniques and prosthesis designs for Total Knee Arthroplasty (TKA) are continually being refined. Despite these advancements, postoperative complications remain a significant challenge in the medical field, with deep vein thrombosis (DVT) in the lower extremity remain prevalent and present a significant challenge in the medical field [1]. DVT not only increases the risk of potentially fatal pulmonary embolism but also conforms to Virchow's triad, which includes stasis of blood flow - often due to factors such as patient age and reduced mobility from pain - hypercoagulability, and vascular endothelial injury. Such injuries may occur during aggressive surgical maneuvers like dislocation, osteotomy, or direct vascular damage. Collectively, these factors significantly elevate the risk of DVT during the perioperative period of TKA [2]. Research indicates that in the absence of anticoagulation therapy, the incidence of DVT post-TKA can vary from 40% to 84% [3]. DVT can result in mild to severe symptoms, including limb swelling and pain, impaired knee function, extended hospital stays, and increased healthcare costs. Hence, early prevention of DVT after TKA is of paramount importance.

The current standard for preventing thrombosis after major othopedic surgeires involves the

https://doi.org/10.62347/VUAI5958

administration of low molecular weight heparin (LMWH) [3]. As an aminodextran sulfate with a molecular weight of 4,000-5,000, LMWH acts by influencing factors Xa and II (the natural anticoagulant antithrombin III) within the coagulation cascade. Administered subcutaneously, LMWH achieves a bioavailability exceeding 90% and reduces the incidences of post-surgical DVT to 5%-10% [4, 5].

Despite LMWH's advantages over unfractionated heparin-including superior bioavailability, greater selectivity, and more precise anticoagulant effects-it is not devoid of limitations. Its an anticoagulant action primarily enhances the inhibition of coagulation factors Xa and antithrombin II, potentially increasing postoperative bleeding. Furthermore, LMWH can bind with hemoglobin and platelets, possibly leading to complications such as thrombocytopenia or anemia. Additionally, the complex interplay between thrombosis and inflammation suggests that inflammation can enhance blood hypercoagulability, further increasing the risk of thrombosis, and vice versa. The anti-inflammatory molecular mechanisms of LMWH remain unclear, and its subcutaneous administration may cause discomfort, ecchymosis, or hematoma, thereby affecting patient compliance.

Safflower yellow (SY), extracted from the traditional Chinese herb safflower, has been used to activate blood circulation, eliminate blood stasis, and clear blood vessels [6]. Clinically, SY has been clinically utilized to treat conditions associated with blood stasis, such as amenorrhea, abdominal pain, chest pain, and symptoms arising from traumatic injury. Recent pharmacological research indicates that SY can effectively inhibit platelet aggregation, alleviate vascular spasms, increase myocardial blood supply, and exhibit analgesic and anti-inflammatory properties [7-10]. It is extensively applied in the prevention and treatment of thrombotic diseases, coronary heart disease, and other conditions like vascular embolism.

Despite preliminary clinical evidence suggesting that the combination of SY with LMWH could reduce the incidence of DVT following orthopedic surgery, there is a lack of systematic reviews consolidating this evidence. This study aims to systematically review randomized controlled trials (RCTs) that have investigated the combination of SY and LMWH in preventing DVT post orthopedic-surgery, thereby providing evidence-based insights for clinical practice [8].

Materials and methods

Inclusion criteria

(1) The research design was RCT; (2) The subjects of study were orthopedic surgery patients with normal coagulation function before surgery; (3) The controls received LMWH, and the study group received the combination of SY and LMWH; (4) The main observation indicators were the incidence of DVT, APTT, PT, etc. within two weeks after surgery.

Exclusion criteria

(1) Not a RCT; (2) Data unavailability; (3) Repeated publications; (4) The full text of the article could not be obtained.

Retrieval procedures

Literature investigations were conducted by using Chinese and English search terms across multiple databases. In Chinese databases such as Chinese Biomedical Literature Database, CNKI Database, Chinese Journal Full-text Database and Wanfang Database, terms like "thrombus, safflower yellow, low molecular weight heparin" were used. For English dababases including PubMed, Cochrane Library, and EMbase, terms used "Safflower Yellow, Deepvein thrombosis, Low molecular heparin". The search was broadened by manual searches in relevant professional journals, and by reviewing references of included literature, covering literature published from January 2000 to March 2024.

Data extraction and quality evaluation

The data extraction was systematically conducted by two independent reviewers who initially screened identified literature based on their titles and abstracts to exclude non-experimental and irrelevant studies. Subsequently, full texts of the potential articles were thoroughly examined to confirm their eligibility. The extracted data encompassed study design, participant demographics, intervention specifics, duration of treatment, and the main outcome measures such as the incidence of DVT, APTT, and PT levels. Any discrepancies encoun-

Table 1. Comprehensive diagnostic criteria for deep vein thrombosis (DVT) based on clinical symptoms and color doppler ultrasound findings

Category	Main Diagnostic Criteria	Secondary Diagnostic Criteria
Clinical Symptoms	1. Sudden onset of pain, swelling, or severe discomfort in the limbs, with marked tenderness in the femoral triangle or calf.	1. Internal diameter of vein increases by less than 10% during Valsalva maneuver.
	2. Extensive swelling of the affected limb.	2. Widening or narrowing of the vein's internal diameter.
	3. Skin of the affected limb appears dark red and temperature rises.	3. Formation of collateral circulation around the veins.
	4. Prominent distension of superficial veins in the affected limb.	
	5. Positive Homan's sign (pain in the calf when the foot is dorsiflexed).	
Color Doppler Ultrasound Findings	1. Presence of a solid echo within the venous lumen in the thrombotic segment.	
	2. Incompressibility of the venous lumen at the site of the thrombus.	
	3. Filling defect in the blood flow signal within the venous lumen, observed during ultrasound examination.	
	4. Loss of phasicity in the blood flow spectrum.	
	5. Altered blood flow distal to the thrombus (enhanced, absent, or diminished).	

terd during data extraction were resolved through discussion with a third reviewer. The methodological quality of the included studies was rigorously assessed using the modified Jadad scale, which evaluates key aspects of study methodology, such as the randomization process, the allocation concealment, the blinding of participants and personnel, the number of participants enrolled in the study, and the documentation of withdrawals and losses to follow-up. Each study was scored, and higher scores indicated better methodological quality which helped identify potential sources of bias and to ensure the reliability of the results synthesized.

Outcome measures

The primary outcomes of interest in this meta-analysis were the incidence of DVT after orthopedic surgery and the efficacy of the combined treatment (SY and LMWH) compared to the control treatment (LMWH alone). DVT was diagnosed based on clinical symptoms and confirmed by color Doppler ultrasound according to predefined criteria (**Table 1**). Secondary outcomes included the assessment of coagulation parameters, specifically the activated partial thromboplastin time (APTT) and prothrombin time (PT), which were measured to evaluate the anticoagulant effects of the treatments. Additionally, the incidence of adverse reactions, including bleeding events and thrombocytopenia, was documented as a measure of treatment safety. The primary and secondary outcomes were assessed at specific time points post-surgery, typically within the first 7 days, to capture the early effects of the interventions on DVT formation and coagulation status. Data on outcomes were extracted from the included studies by two independent reviewers, with a third reviewer involved in case of disputes. Intention-to-treat data were collected whenever available to minimize bias.

Statistical analysis

The statistical analysis for this meta-analysis was conducted using RevMan 5.3 software, with additional analyses performed in STATA. Heterogeneity among the studies was assessed using the I^2 statistic and Cochran's Q test, considering significant heterogeneity at an I^2 value over 50% or a P-value < 0.1. Depending on the

Table 2. Summary of intervention studies on treatment efficacy

literature	Group	Sample size n	Interventions	Course of treatment	Main outcome indicators	Jadad score
Literature1	control	50	a	7 days	1), 2,) 5)	2
	combined	50	a+b			
Literature2	control	43	a	12 days	2), 4)	2
	combined	43	a+b			
Literature3	control	30	a	14 days	1), 4)	1
	combined	30	a+b			
Literature4	control	30	a	14 days	1), 3), 4)	3
	combined	30	a+b			
Literature5	control	60	a	14 days	1), 5)	1
	combined	60	a+b			
Literature6	control	40	a	14 days	1)	3
	combined	40	a+b			
Literature7	control	40	a	21 days	3), 4)	4
	combined	40	a+b			
Literature8	control	20	a	14 days	1), 2), 4)	2
	combined	20	a+b			

presence of heterogeneity, results from studies were combined using either a fixed-effects or a random-effects model. Risk ratios (RR) with 95% confidence intervals (CI) were calculated for dichotomous outcomes like the incidence of DVT, and mean differences (MD) with 95% CI were computed for continuous outcomes like APTT and PT levels. Sensitivity analyses and subgroup analyses were conducted to explore sources of heterogeneity and to test the robustness of the findings. Publication bias was assessed using funnel plots as well as Egger's and Begg's tests. A *P*-value < 0.05 was considered significant for the primary outcomes, while a *P*-value < 0.1 was used for assessing publication bias. The study follows PRISMA 2020 and the research process is shown in Figure S1.

Results

A total of 165 relevant papers were obtained from initial search. By reviewing abstracts and full texts to ensure alignment with our inclusion criteria, eight RCTs were included in this meta-analysis. These studies encompassed a total of 626 patients, with 313 patients receiving the combined treatment of SY and LMWH, and 313 serving as controls [11-18]. Seven of these studies assessed the incidence of DVT, while five studies reported on APTT and PT. Remarkably, there were no patients lost to follow-up in any of the eight studies. The methodological quality, of the included studies was assessed using the modified Jadad scale. One study achieved a high reliability score of 4 points. The remaining studies were scored between 1 and 3 points, indicating variability in study quality. Detailed information about the study characteristics and their quality evaluation are summarized in **Table 2**.

Incidence of DVT

Seven studies involving 548 patients were included to evaluate the incidence of DVT. The analysis showed no statistical heterogeneity among the study results (P=0.69, 1=0%). Therefore, a fixed effect model was selected for the meta-analysis, and the results indicated that the incidence of DVT was lower in the group receiving combined treatment (**Figure 1**).

A total of 5 studies compared postoperative changes of APTT, and heterogeneity was found among the studies. Therefore, a random effect model was selected for analysis. The results showed that the APTT level was improved in the group received combined treatment (**Figure 2**).

A total of 5 studies compared changes of postoperative PT, and heterogeneity was identified among the studies. Thus, a random effect model was utilized for analysis. The results displayed that level of APTT was enhanced in the group receiving combined treatment (**Figure 3**).

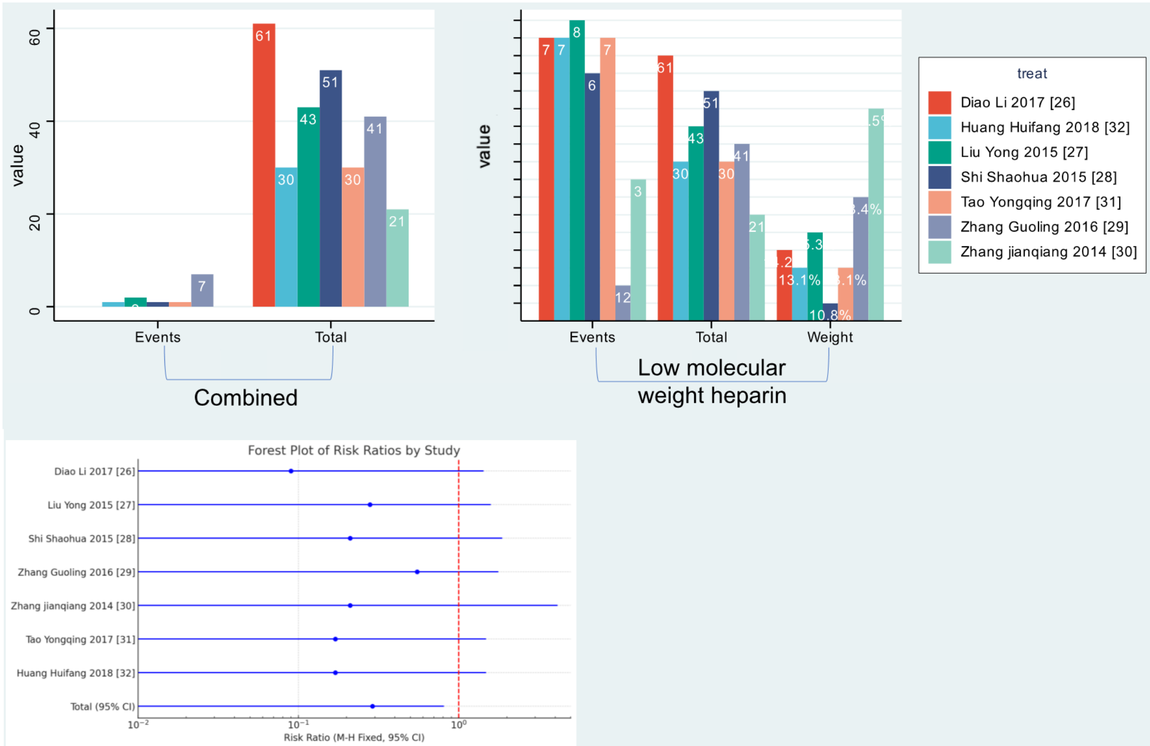

Figure 1. The incidence of DVT and (forest plot) comparison of postoperative DVT incidence of patients.

Discussion

The incidence of DVT following orthopedic surgery, such as TKA, poses a significant threat to patient health and can potentially leading to life-threatening conditions like pulmonary embolism [19-21]. Our meta-analysis aimed to evaluate the efficacy and safety of combining SY with LMWH for the prevention of DVT in this context. Including eight of RCTs with a total of 624 patients, our findings demonstrate indicate that the combination treatment significantly reduced the incidence of DVT compared to LMWH alone. This aligns with previous clinical studies that have highlighted the benefits of SY in reducing DVT incidence [7, 22].

SY has the effect to activate blood circulation, remove blood stasis, and clear blood vessels [25]. Pharmacological studies have demonstrated that SY can inhibit platelet aggregation, relieve vascular spasm, increase myocardial blood supply, and possesses analgesic and anti-inflammatory effects [26]. These properties may complement the anticoagulant action of LMWH, providing a more comprehensive approach for thromboprophylaxis.

The pathogenesis of DVT after TKA can be explained by Virchow's triad, which includes venous stasis, vascular endothelial injury, and a hypercoagulable state [23, 24]. Patients undergoing TKA frequently exhibit these risk factors, which are exacerbated by reduced mobility, intraoperative injury, and advanced age, thereby elevating their susceptibility to DVT [25]. Although LMWH has been the a staple in thromboprophylaxis after major orthopedic surgery due to its high bioavailability, selectivity, and precision anticoagulation capabilities, it is not devoid of limitations, such as potential for increased postoperative postoperative bleeding and unresolved questions regarding its anti-inflammatory effects [23]. The potential mechanisms by which SY enhances the efficacy of LMWH are complex and likely multifactorial. SY's traditional use in activating blood circulation and removing blood stasis aligns with modern pharmacological findings that it inhibits platelet aggregation and relieves vascular spasm [25, 26]. These effects could complement LMWH's action on coagulation factors, creating a synergistic effect that enhances overall thromboprophylaxis. The anti-inflammatory properties of SY may also play a

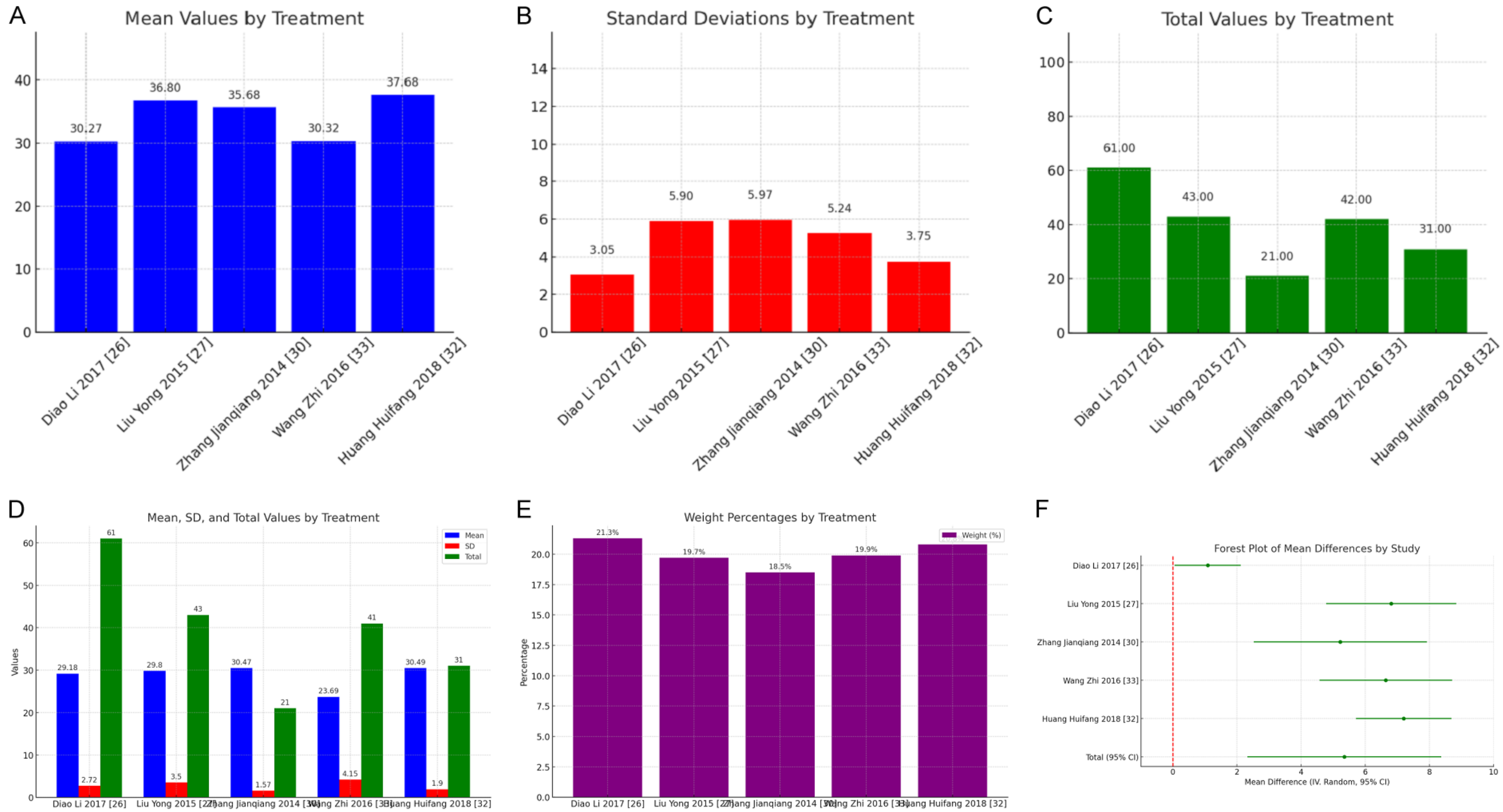

Figure 2. Postoperative changes in APTT (A-C) represent combined. (D, E) represent for low molecular weight heparin and (F) comparison of postoperative APTT in patients.

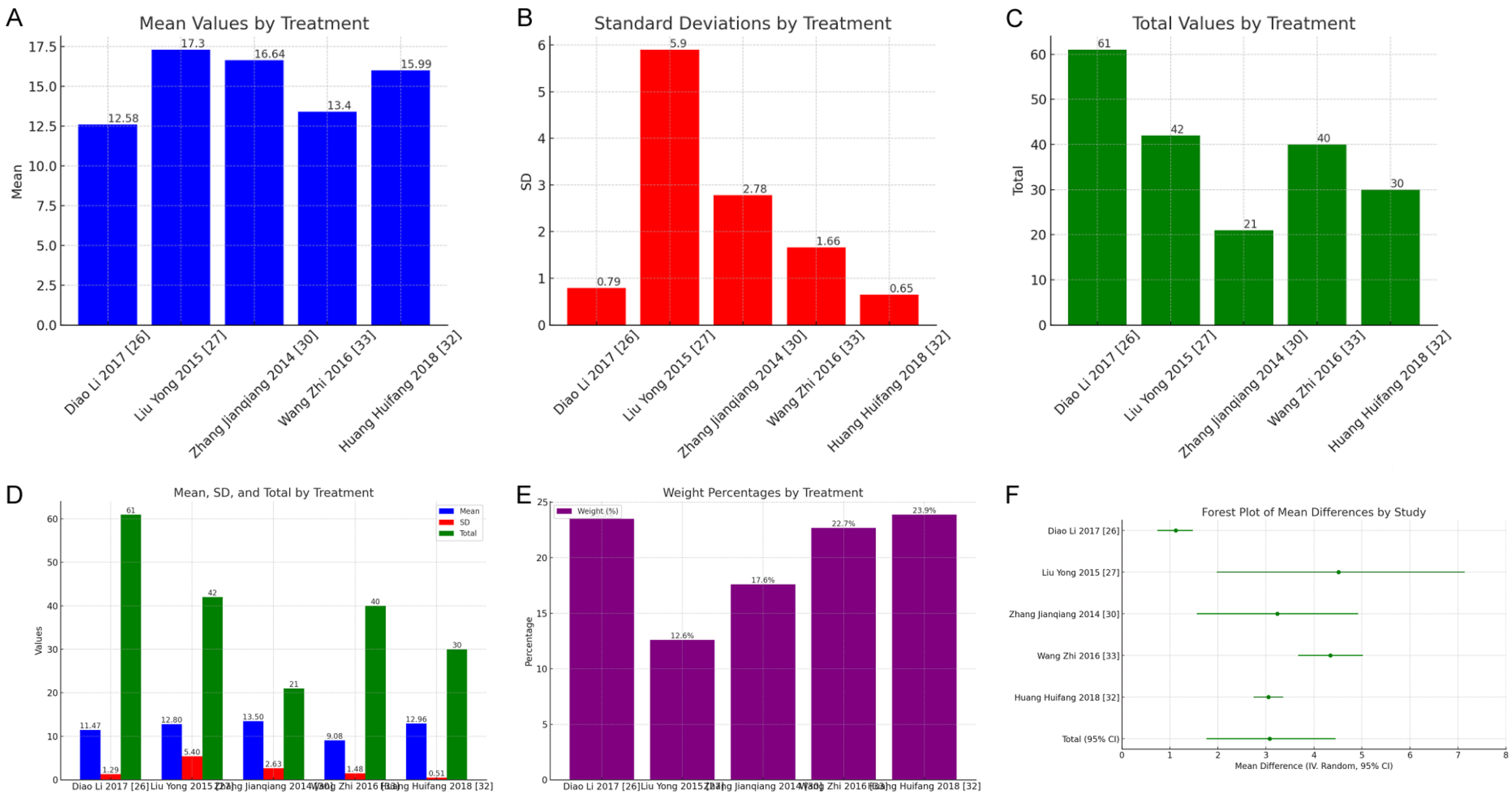

Figure 3. Postoperative PT in patients (A-C) represent combined. (D, E) represent for low molecular weight heparin and (F) comparison of postoperative PT in patients.

crucial role, as inflammation is a key component in the pathogenesis of DVT [23, 24]. By modulating the inflammatory response, SY could reduce the hypercoagulable state that often follows surgery. The addition of SY may mitigate the drawbacks of LMWH, offering a balanced approach that maximizes the benefits while minimizing the risks. This is in contrast to alternative anticoagulants, which may have different safety profiles and may not provide the same level of synergistic benefit as SY.

The safety and tolerability of the combined treatment are of paramount importance, especially considering the delicate balance between effective thromboprophylaxis and the risk of bleeding. Our findings suggest that the addition of SY to LMWH does not increase the incidence of adverse reactions, which is a significant advantage over other anticoagulant therapies that may have a higher risk of bleeding [27-29]. This could lead to improved patient outcomes and satisfaction, as well as reduced healthcare costs associated with managing bleeding complications.

Despite the promising results, several limitations of our study must be considered. The variability in study quality, assessed by the modified Jadad scale, and the heterogeneity among the included studies might affect the robustness and generalizabitlity of our findings [29-32]. Additionally, the majority of the studies were conducted within similar demographic and healthcare settings, which may not fully represent the broader patient population undergoing orthopedic surgery.

Further investigation into the clinical significance of our findings is necessary. While the reduction in postoperative bleeding with the combined treatment is promising, the exact mechanisms underlying this effect are not fully understood and warrant further research [33]. Longitudinal studies with extended follow-up periods could provide insights into the long-term safety and efficacy of the combined therapy.

Future research should focus on validating these findings across a more diverse patient population and in various healthcare settings to determine the consistency of the observed benefits. Exploring the optimal dosing and timing for the administration of SY and LMWH in combination is also crucial to maximize the therapeutic benefits while minimizing potential adverse effects. The economic implications of the combined therapy should also be considered. While the upfront costs of adding SY to LMWH may be higher, the potential reduction in DVT incidence and associated complications could result in cost savings in a long run. Health policy makers should take these factors into account when developed guidelines for thromboprophylaxis in orthopedic surgery.

From a patient-centered perspective, the combined treatment could offer a more holistic approach to thromboprophylaxis. The potential for reduced postoperative pain and improved comfort, as suggested by the analgesic and anti-inflammatory effects of SY, could enhance patient satisfaction and recovery experiences. Future research should incorporate patient-reported outcomes to better understand the impact of the combined treatment on patients' quality of life.

In conclusion, our meta-analysis suggests that the combination of SY and LMWH is more effective in preventing DVT after orthopedic surgery than LMWH alone, with no significant increase in adverse reactions. This provides a promising direction for the development of thromboprophylactic strategies. However, these findings should be interpreted with caution, and further high-quality research is warranted to clarify the potential benefits and mechanisms of this combination. Applying SY with LMWH can be a promising strategy that enhances thromboprophylaxis in orthopedic surgery, offering a valuable addition to the existing armamentarium of treatments.

Acknowledgements

This study was supported by the Self-selected project in Yan'an Hospital affiliated to Kunming Medical University (yyky019-040).

Disclosure of conflict of interest

None.

Address correspondence to: Hong Xu, Department of Pharmacy, Kunming Medical University Affiliated Yan'an Hospital, Kunming 650051, Yunnan, China. E-mail: 18313785136@163.com

References

[1] Alhag SK, Al-Mekhlafi FA, Abutaha N, Abd Al Galil FM and Wadaan MA. Larvicidal potential

of gold and silver nanoparticles synthesized using Acalypha fruticosa leaf extracts against Culex pipiens (Culicidae: Diptera). J Asia Pac Entomol 2021; 24: 184-189.
[2] Abd Al Galil FM, Al-Keridis LA, Al-Mekhlafi FA, Al-Shuraym LA, Alhag SK, Mohamed RAEH and Wadaan MA. Growth and development of Chrysomya saffranea (Diptera: Calliphoridae) in response to different food substrates. Entomol Res 2021; 51: 528-532.
[3] Abd Algalil FM and Zambare SP. Effects of temperature on the development of Calliphorid fly of forensic importance Chrysomya megacephala (Fabricius, 1794). Indian J Appl Res 2015; 5: 767-769.
[4] Dragoman MV, Tepper NK, Fu R, Curtis KM, Chou R and Gaffield ME. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. Int J Gynaecol Obstet 2018; 141: 287-294.
[5] Aguiar de Sousa D, Lucas Neto L, Canhão P and Ferro JM. Recanalization in cerebral venous thrombosis: a systematic review and meta-analysis. Stroke 2018; 49: 1828-1835.
[6] Khan J, Schmidt RL, Spittal MJ, Goldstein Z, Smock KJ and Greene DN. Venous thrombotic risk in transgender women undergoing estrogen therapy: a systematic review and meta-analysis. Clin Chem 2019; 65: 57-66.
[7] Cui CJ, Wang GJ, Yang S, Huang SK, Qiao R and Cui W. Tissue factor-bearing MPs and the risk of venous thrombosis in cancer patients: a meta-analysis. Sci Rep 2018; 8: 1675.
[8] Bundhun PK, Soogund MZS and Huang F. Arterial/venous thrombosis, fetal loss and stillbirth in pregnant women with systemic lupus erythematosus versus primary and secondary antiphospholipid syndrome: a systematic review and meta-analysis. BMC Pregnancy Childbirth 2018; 18: 212.
[9] Wang X, Xu Y, Chu C, Li H, Mi J, Wen Z, Zhang S, Wang Q and Quan S. Effect of safflower yellow on early type II diabetic nephropathy: a systematic review and meta-analysis of randomized controlled trials. J Pediatr Endocrinol Metab 2019; 32: 653-665.
[10] Bao LD, Wang Y, Ren XH, Ma RL, Lv HJ and Agula B. Hypolipidemic effect of safflower yellow and primary mechanism analysis. Genet Mol Res 2015; 14: 6270-6278.
[11] Diao L, Li H, Wang SM, Zhao M, Zhao SH, Tian BT and Zhao G. Observation on the efficacy of safflower yellow pigment sodium chloride injection in preventing deep vein thrombosis of lower limbs after fracture surgery. Hebei Med J 2017; 39: 1706-1708.
[12] Liu Y, Li Y and Guan JZ. Analysis of safflower yellow pigment combined with low molecular weight heparin calcium in preventing deep vein thrombosis of lower limbs after orthopedic surgery. North Pharm 2015; 1: 161-162.
[13] Shi SH, Lv SJ and Li LD. Effect of low molecular weight heparin combined with safflower yellow pigment on perioperative platelet and endothelial cell function in patients with lower limb fracture. China Pharm Industry 2015; 24: 82-83.
[14] Zhang GL, Zhang XL and Zhang X. Analysis of the efficacy of safflower yellow pigment in preventing deep vein thrombosis of lower limbs in 40 cases. J Armed Police Logis Acad (Med Edit) 2016; 25: 149-150.
[15] Zhang JQ. Clinical observation of safflower yellow pigment injection combined with low molecular weight heparin calcium in preventing deep vein thrombosis of lower limbs after hip replacement. Hunan J Tradit Chin Med 2014; 30: 71-72.
[16] Tao YQ. Clinical observation of safflower yellow pigment combined with low molecular weight heparin in preventing deep vein thrombosis in bedridden patients after fracture surgery. Electr J Clin Med Literat 2017; 4: 18751-18752.
[17] Huang HF and Lin YX. Preventive effect of safflower yellow pigment combined with low molecular weight heparin in deep vein thrombosis of lower limbs after hip fracture surgery. Thromb Hemostasis 2018; 24: 31-33.
[18] Wang Z, Yang WX, Zhang XH and Jiang X. Effects of safflower yellow pigment sodium chloride injection on blood rheology and coagulation function in patients undergoing hip arthroplasty. J Hainan Med College 2016; 22: 1684-1687.
[19] Zhang L, Zhou Z, Zhai W, Pang J, Mo Y, Yang G, Qu Z and Hu Y. Safflower yellow attenuates learning and memory deficits in amyloid β-induced Alzheimer's disease rats by inhibiting neuroglia cell activation and inflammatory signaling pathways. Metab Brain Dis 2019; 34: 927-939.
[20] Lyu X, Yan K, Xu H, Zhu H, Pan H, Wang L, Yang H and Gong F. Intragastric safflower yellow and its main component HSYA improve leptin sensitivity before body weight change in diet-induced obese mice. Naunyn Schmiedebergs Arch Pharmacol 2022; 395: 579-591.
[21] Fu H, Liu X, Jin L, Lang J, Hu Z, Mao W, Cheng C and Shou Q. Safflower yellow reduces DEN-induced hepatocellular carcinoma by enhancing liver immune infiltration through promotion of collagen degradation and modulation of gut microbiota. Food Funct 2021; 12: 10632-10643.
[22] Yang XW, Li YH, Zhang H, Zhao YF, Ding ZB, Yu JZ, Liu CY, Liu JC, Jiang WJ, Feng QJ, Xiao BG and Ma CG. Safflower yellow regulates microg-

lial polarization and inhibits inflammatory response in LPS-stimulated Bv2 cells. Int J Immunopathol Pharmacol 2016; 29: 54-64.
[23] Ma Q, Ruan YY, Xu H, Shi XM, Wang ZX and Hu YL. Safflower yellow reduces lipid peroxidation, neuropathology, tau phosphorylation and ameliorates amyloid β-induced impairment of learning and memory in rats. Biomed Pharmacother 2015; 76: 153-164.
[24] Fu H, Wu R, Li Y, Zhang L, Tang X, Tu J, Zhou W, Wang J and Shou Q. Safflower yellow prevents pulmonary metastasis of breast cancer by inhibiting tumor cell invadopodia. Am J Chin Med 2016; 44: 1491-1506.
[25] Ghorbani E, Hasani Keleshteri R, Shahbazi M, Moradi F and Sadri M. Optimization of extraction yield of carthamine and safflower yellow pigments from safflower (Carthamus tinctorious L.) under different treatments and solvent systems. Res J Pharmacognosy 2015; 2: 17-23.
[26] Jadhav BA and Joshi AA. Extraction and quantitative estimation of bio active component (yellow and red carthamin) from dried safflower petals. Indian J Sci Technol 2015; 8: 1-5.
[27] Moik F, Posch F, Zielinski C, Pabinger I and Ay C. Direct oral anticoagulants compared to low-molecular-weight heparin for the treatment of cancer-associated thrombosis: updated systematic review and meta-analysis of randomized controlled trials. Res Pract Thromb Haemost 2020; 4: 550-561.
[28] Li A, Garcia DA, Lyman GH and Carrier M. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): a systematic review and meta-analysis. Thromb Res 2019; 173: 158-163.
[29] Shi C, Wang C, Wang H, Yang C, Cai F, Zeng F, Cheng F, Liu Y, Zhou T, Deng B, Vlodavsky I, Li JP and Zhang Y. The potential of low molecular weight heparin to mitigate cytokine storm in severe COVID-19 patients: a retrospective cohort study. Clin Transl Sci 2020; 13: 1087-1095.
[30] Mattioli M, Benfaremo D, Mancini M, Mucci L, Mainquà P, Polenta A, Baldini PM, Fulgenzi F, Dennetta D, Bedetta S, Gasperoni L, Caraffa A and Frausini G. Safety of intermediate dose of low molecular weight heparin in COVID-19 patients. J Thromb Thrombolysis 2021; 51: 286-292.
[31] Martinelli I, Ciavarella A, Abbattista M, Aliberti S, De Zan V, Folli C, Panigada M, Gori A, Artoni A, Ierardi AM, Carrafiello G, Monzani V, Grasselli G, Blasi F and Peyvandi F. Increasing dosages of low-molecular-weight heparin in hospitalized patients with Covid-19. Intern Emerg Med 2021; 16: 1223-1229.
[32] Pavoni V, Gianesello L, Pazzi M, Stera C, Meconi T and Frigieri FC. Venous thromboembolism and bleeding in critically ill COVID-19 patients treated with higher than standard low molecular weight heparin doses and aspirin: a call to action. Thromb Res 2020; 196: 313-317.
[33] Zhou MX, Fu JH, Zhang Q and Wang JQ. Effect of hydroxy safflower yellow A on myocardial apoptosis after acute myocardial infarction in rats. Genet Mol Res 2015; 14: 3133-3141.

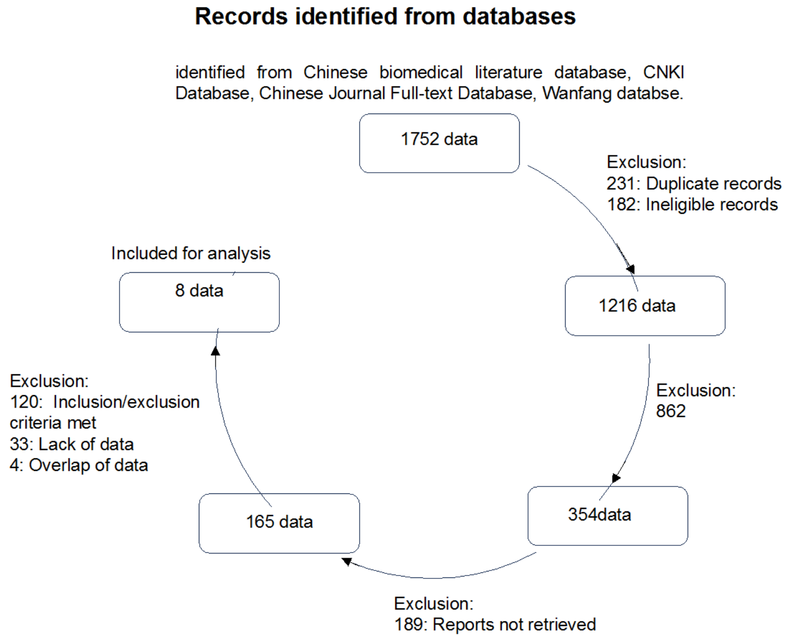

Figure S1. Research flow chart.