Original Article

The safety profile of preoperative administration of heparin for thromboprophylaxis in Chinese patients intended for thoracoscopic major thoracic surgery: a pilot randomized controlled study

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Background: Patients undergoing major thoracic surgery especially for cancers are at a high risk of perioperative thromboembolism. Current guidelines recommended either heparin sodium (unfractionated heparin) or low-molecular-weight heparin (LMWH) for those patients at high risk of deep vein thrombosis (DVT). However, the rational timing of starting heparin has not yet been well established, because DVT can be caused by not only surgery but also comorbidities as well as prolonged hospital stay, and thoracic surgeons always concerned about heparin-related increased risk of intra- or post-operative bleeding. Therefore, this study aimed to establish the safety profile of preoperative administration of heparin for thromboprophylaxis in Chinese patients intended for thoracoscopic major thoracic surgery.

Methods: From June to August 2016, patients intended for thoracoscopic lobectomy, esophagectomy, and thymectomy were randomly assigned into two groups: the case group (starting heparin sodium 5,000 U, bid preoperatively upon the admission into our department) and the control group (starting heparin sodium 5,000 U, bid postoperatively from postoperative day 1). The baseline data including demographic data and preoperative conditions were collected. The end points included operation time, intraoperative bleeding volume, postoperative chest tube drainage volume and duration as well as lab coagulation function data.

Results: A total of 58 qualified patients were randomized into case group (29 patients) and control group (29 patients), and after excluding 6 conversion patients, the case group and control group each had 26 patients for analysis. The baseline data of the two groups were comparable. Operation time (P=0.368), intraoperative bleeding volume (P=0.231), postoperative drainage days (P=0.466), and mean drainage volume per day (P=0.108) were not significantly increased in case group compared with those of control group. Moreover, there were no significant differences of perioperative coagulation function between these two groups.

Conclusions: Preoperative administration of heparin for thromboprophylaxis in Chinese patients intended for thoracoscopic major thoracic surgery was safe and feasible.

Trial registration: NCT02940444 (https://register.clinicaltrials.gov/).

Keywords: Preoperative; postoperative; heparin; thromboprophylaxis; thoracic surgery; safety

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Introduction

Venous thromboembolism (VTE), mainly consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third commonest cause of cardiovascular death after myocardial infarction and stroke with high morbidity and mortality (1,2). Patients who underwent major thoracic surgery including lobectomy, pneumonectomy, esophagectomy are often at a higher risk for VTE (3). The incidence of VTE for patients following major thoracic surgery was estimated to be as high as 19–26% (4). Even though American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommended routine VTE prophylaxis with either heparin sodium (unfractionated heparin) or low-molecular-weight heparin (LMWH) for those high risk patients after thoracic surgery, the rational timing and dose of heparin thromboprophylaxis is still lack of consensus (5,6). Recent researchers have found that even though patients who underwent thoracic surgery received thromboprophylaxis postoperatively there was still chance of VTE after thoracic surgery (7,8). Therefore, some investigators have raised the doubt that whether postoperative heparin once or twice a day could provide sufficient thromboprophylaxis for patients following major thoracic surgery (5). Moreover, many patients underwent major thoracic surgery for cancer, and cancer patients were reported to be about 5- to 7-fold higher risk of VTE compared with normal population (9). Cancer patients were also found to be more than threefold of risk of fatal PE than non-cancer patients undergoing similar thoracic surgery (10). Therefore, there is an urgent need for investigating the rational timing and dose of heparin for thromboprophylaxis in patients intended for thoracic surgery. Due to the special medical conditions in China, patients intended for thoracic surgery usually need an average preoperative time of 3–5 days for surgery preparation after hospital admission, not the same as those in western countries who undergo surgery at the day of admission, and different human races have different risks of DVT, which indicated a need of specific plan of thromboprophylaxis for Chinese patients. Since American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommended starting heparin as thromboprophylaxis of orthopedic surgery 12 h or more preoperatively (11), we therefore believe that preoperative administration of heparin for thromboprophylaxis in major thoracic surgery is still reasonable and safe. As there is no relevant study available, we conducted this pilot randomized controlled trial to explore the safety profile of preoperative administration of heparin as thromboprophylaxis for Chinese patients intended for thoracoscopic major thoracic surgery. To our knowledge, this is the first study to explore the safety profile of preoperative administration of heparin for thromboprophylaxis in patients intended for thoracoscopic major thoracic surgery.

Methods

Patients

Our current study was conducted prospectively and approved by the Ethics Committee of West China Hospital, Sichuan University (approval number: 20160601). Patients who were intended to receive thoracoscopic major thoracic surgery (including lobectomy, esophagectomy, and thymectomy) under general anesthesia in our hospital from June 2016 to August 2016 were recruited in our study. Written informed consent was obtained from each patient before taking part in our study. All those patients were routinely screened for VTEs by ultrasound before hospital admission. The inclusion criteria were as follow: (I) 18–75 years old without any preoperative VTEs; (II) patients intended for video-assisted thoracoscopic major thoracic surgery (including lobectomy, esophagectomy, and thymectomy). The exclusion criteria included: (I) patients with coagulation disorders: preoperative international normalized ratio (INR) >1.5, or blood platelet count $<50\times10^9$/L; (II) patients receiving any therapeutic anticoagulation preoperatively; (III) patients undergoing planned open thoracic surgery; (IV) patients with severe renal or liver dysfunction.

Procedure

This is a single center study conducted in the Department of Thoracic Surgery, West China Hospital, Sichuan University from May 2016 to August 2016. All those included patients were treated by one single surgical team (directed by Dr. Lin) and were randomly assigned into two groups by computer after admission into our department: the case group started heparin sodium (5,000 U, bid) rightly after admission and continued until discharge, and the control group started heparin sodium (5,000 U, bid) from the first postoperative day and also continued until discharge. If the postoperative drainage volume exceeded 500 mL per day, heparin sodium would be temporally ceased and

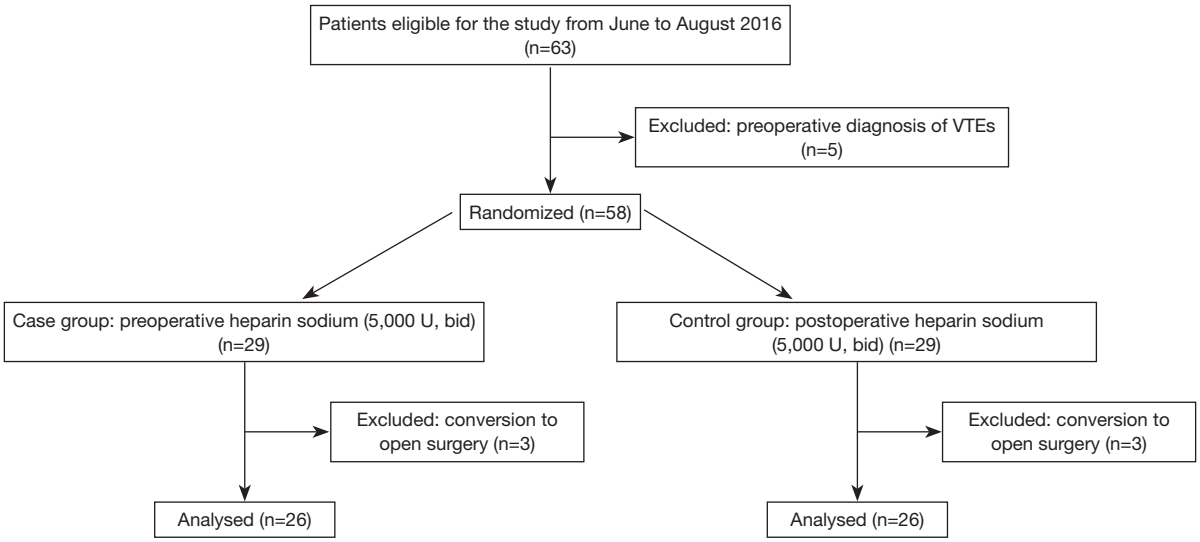

Figure 1 A flow chart of the trial. VTEs, venous thromboembolisms.

re-started when the drainage volume was less than 500 mL per day in both groups. The indications for remove of chest tube was the same in both groups: (I) for lobectomy and thymectomy, if the chest tube drainage volume was less than 250 mL/day, without air leak, the tube would be removed; (II) for esophagectomy, the chest tube would be removed if the drainage volume was less than 250 mL/day after oral intake begins (usually on postoperative day 6). All those patients were again routinely screened for VTEs rightly after remove of chest tube.

Data for analysis

The baseline data including demographic data as well as preoperative coagulation function data [blood platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), and INR] and major comorbidities of those included patients (including high blood pressure, diabetes, hyperlipidemia, mild to moderate narrow in coronary artery, and arrhythmia) were collected and compared. The end points included operation time and data for postoperative coagulation function as well as data of intraoperative bleeding volume and postoperative chest tube drainage (collected by other colleagues in our department who were outside of the trial).

Statistical analysis

Statistical analysis was performed using SPSS 22.0 software (SPSS Corp., Chicago, IL, USA). Data were represented as the mean ± standard deviation for continuous variables or number (%) for categorical data. For continuous variables, Student's test was applied; while for categorical data, the chi-square or Fisher's exact test was applied. A two-sided P value less than 0.05 was considered statistically significant.

Results

Baseline level characteristics of the included patients

A flow chart of the recruitment of those patients was shown in *Figure 1*. A total of 58 patients who met the inclusion criteria were randomized into case and control groups upon the admission day by computer: 29 patients in case group and 29 patients in control group. All of those patients intended to undergo thoracoscopic major thoracic surgery (consisting of lobectomy, esophagectomy, and thymectomy). Six patients who were converted to open surgery were excluded from analysis because the intraoperative bleeding volume had been greatly influenced by their conditions of severe pleural adhesion or bleeding happened in dissecting the major vessels invaded by the tumor. The baseline characteristics of those included patients in both group were comparable, and major comorbidities of the patients in each group were also similar (*Table 1*).

Safety profile of preoperative administration of heparin for patients undergoing thoracoscopic major thoracic surgery

The intraoperative and postoperative characteristics for each

Table 1 Baseline characteristics of the patients in both case group and control group

Characteristics	Case group (n=26)	Control group (n=26)	P value
Sex (male/female)	22/4	17/9	0.109
Age (mean ± SD)	59.2±9.7	56.8±8,4	0.347
Preoperative PLT counts (×10^9/L)	178.0±67.5	176.4±53.1	0.928
Preoperative PT (s)	11.5±0.7	11.4±0.7	0.557
Preoperative APTT (s)	27.0±3.5	28.2±3.3	0.222
Preoperative INR	0.97±0.06	0.96±0.06	0.721
Surgical procedures			0.918
VATS lobectomy	19	18	
MIE	4	4	
VATS thymectomy	3	4	
Comorbidity*			0.578
Yes	13	15	
No	13	11	

*, including high blood pressure, diabetes, hyperlipidemia, mild to moderate narrow in coronary artery, and arrhythmia. SD, standard deviation; PLT, platelet; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; VATS, video-assisted thoracoscopic surgery; MIE, minimally invasive esophagectomy.

Table 2 Safety profile of preoperative administration of heparin in thoracoscopic major thoracic surgery

Characteristics	Case group (n=26)	Control group (n=26)	P value
Preoperative duration of heparin (day)	2.8±3.3	0	P<0.001
postoperative duration of heparin (day)	4.3±1.7	4.5±2.2	0.629
Operation time (min)	154.0±106.1	131.7±66.3	0.368
Intraoperative bleeding (mL)	120.8±84.9	93.1±85.5	0.231
Postoperative PLT count (×10^9/L)	183.1±69.4	165.3±31.2	0.241
Postoperative INR	1.03±0.11	1.00±0.09	0.277
Postoperative drainage time (day)	3.2±1.5	3.5±1.9	0.466
Mean drainage volume per day (mL)	243.0±85.7	200.0±102.8	0.108

PLT, platelet; INR, international normalized ratio.

group were listed in *Table 2*. Although the postoperative duration of the administration of heparin in each group was similar (P=0.629), the preoperative duration was significantly longer in the case group than that in control group (2.8±3.3 and 0 days, respectively; P<0.001). However, the operation time in each group was not significantly different (154.0 and 131.7 min, respectively; P=0.368). Even though the mean intraoperative bleeding tended to be increased in case group compared with control group (120.8 and 92.1 mL), no significant difference was observed (P=0.231). No significant difference was also observed in postoperative INR (1.03 and 1.00, respectively; P=0.227), postoperative platelet count (183.1×10^9/L and 165.3×10^9/L, respectively; P=0.241), and postoperative drainage time (3.2 and 3.5 days, respectively; P=0.466) between these two groups. Moreover, postoperative chest tube drainage volume also showed no significant difference between the two groups (243.0 and 200.0 mL/day, respectively;

P=0.108).

The detailed characteristics of those patients excluded from final analysis due to conversion to open surgery were also presented in *Table 3*. In these patients with open surgery, the intraoperative time and bleeding volume as well as postoperative chest tube drainage volume and duration seemed not to be different in those two groups. Moreover, the coagulation function of those patients undergoing open thoracic surgery was not significantly influenced in the case group as compared with control group.

All of our patients had no major postoperative complications such as severe pulmonary infection, bronchopleural fistula, or anastomosis leakage.

Efficacy of preoperative administration of heparin for thromboprophylaxis in thoracoscopic major thoracic surgery

No VTEs was observed in control group, but there is one case of PE happened in the case group. This 61-year-old male patient was diagnosed with lung cancer and hyperlipidemia, and underwent lobectomy. On postoperative day 2, he suffered transient syncope, and the following computed tomography pulmonary angiography uncovered small embolisms in the pulmonary artery (*Figure 2*). This patient recovered quickly after continued administration of heparin plus warfarin.

Discussion

PE caused by DVT represents a disastrous complication for both surgical and nonsurgical patients. The risk factors associated with VTE included age, bed rest, malignancy, as well as surgical procedures, and so on (12). Therefore, patients undergoing major thoracic surgery especially for cancers were at a relatively high risk of VTE perioperatively (13). Current guidelines have recommended thromboprophylaxis for those high-risk patients (3). As to thoracic surgery, for the fear of increased bleeding during surgical procedures, the thromboprophylaxis often starts postoperatively or 6–12 h before operation. Obviously, this kind of thromboprophylaxis only aims to prevent surgery-induced VTE, lacking of the concerns for prevention of VTE caused by other conditions (for example, age, bed rest, and malignancy). Despite of the postoperative administration of thromboprophylaxis, there was still chance of VTE after thoracic surgery (7,8). Here comes the question: whether postoperative administration of heparin is sufficient for patients undergoing major thoracic surgery and whether prolonging the preoperative time of administration of heparin is reasonable and safe. Recently, American College of Chest Physicians Evidence-Based Clinical Practice Guidelines have recommended starting heparin as thromboprophylaxis of orthopedic surgery 12 hours or more preoperatively (11), and some studies have found that preoperative start LMWH yielded lower mortality rate as compared with postoperative start without any increased risk of bleeding complications in patients with orthopedic surgery (14). Therefore, we hypothesized that preoperative administration of heparin for thromboprophylaxis in major thoracic surgery is reasonable and safe. Herein, we conducted this pilot randomized controlled study to explore the safety profile of preoperative administration of heparin as thromboprophylaxis for patients intended for thoracoscopic major thoracic surgery. To our best knowledge, this is the first study of the current issue.

In our study, we randomized 58 patients who were intended for thoracoscopic major thoracic surgery into case group (the preoperative heparin group) and control group (the postoperative heparin group). The baseline characteristics of both groups were comparable. Preoperative administration of heparin did not significantly increase the operation time. Even though preoperative administration of heparin tended to increase the intraoperative bleeding, it did not show significant difference. Moreover, we believe that a mean intraoperative bleeding volume of 120.8 mL in the preoperative heparin group was rational and acceptable as compared with 92.1 mL in the postoperative heparin group. We also found that preoperative administration of heparin did not influence postoperative coagulation function or increase the chest tube drainage duration time. Moreover, preoperative administration of heparin did not significantly increase the mean drainage volume per day compared with postoperative administration of heparin. The similar results could also be observed in those excluded patients who experienced conversion due to severe pleural adhesion or tumor invasion. Therefore, our study proved that preoperative administration of heparin as thromboprophylaxis for patients intended for major thoracic surgery was safe without significantly increased risk of bleeding (a numeric difference of about 30 mL in intraoperative bleeding). Interestingly, in all of our patients, only one patient started preoperative administration of heparin was incidentally diagnosed with mild PE due to less prominent symptom of transient syncope and he recovered soon from continued

Table 3 Patients excluded from our final analysis due to conversion to open surgery

Group	Sex/age (years)	Surgery	Reason for significant intraoperative bleeding	Duration of preoperative heparin (day)	Duration of postoperative heparin (day)	Operation time (min)	Intraoperative bleeding (mL)	Postoperative INR	Postoperative drainage time (day)	Mean drainage volume per day (mL)
Case group 1	Male/65	Esophagectomy	Severe pleural adhesion	3	7	330	300	1.22	8	302
Case group 2	Male/64	Lobectomy	Severe pleural adhesion	5	5	150	250	0.97	4	430
Case group 3	Female/51	Lobectomy	Bleeding in dissecting the major vessels invaded by the tumor	5	10	140	500	0.90	4	133
Control group 1	Male/53	Lobectomy	Severe pleural adhesion	0	5	190	350	1.07	5	334
Control group 2	Male/55	Lobectomy	Severe pleural adhesion	0	3	140	230	1.13	2	210
Control group 3	Male/63	Lobectomy	Bleeding in dissecting the major vessels invaded by the tumor	0	6	220	300	1.15	3	143

INR, international normalized ratio.

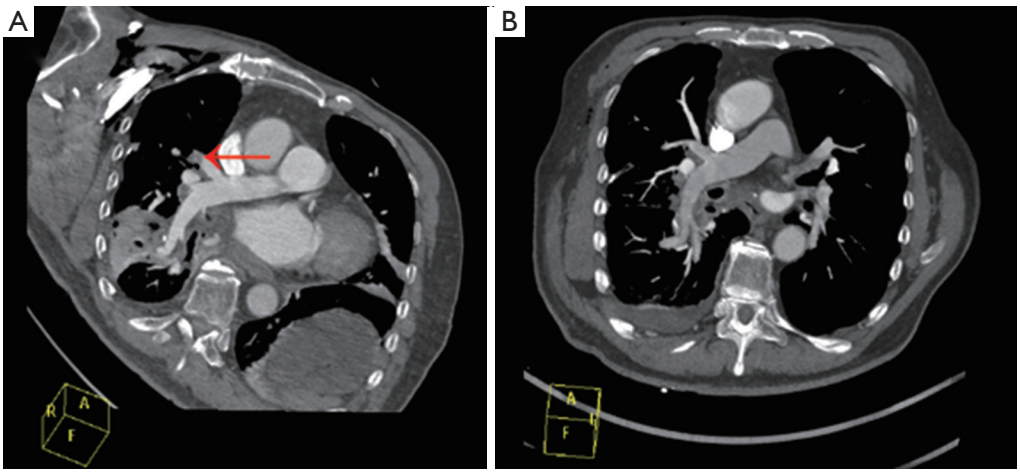

Figure 2 Images of the patient in case group suffering postoperative pulmonary embolism. (A) The computed tomography pulmonary angiography (CTPA) showed small embolisms in the right pulmonary artery on postoperative day 2 (red arrow); (B) the CTPA showed that the embolisms in the right pulmonary artery disappeared in the same patients treated with continued administration of heparin plus warfarin for 5 days.

administration of heparin plus warfarin. Considering the fact that this patient just started heparin only one day before operation, we suspect that if he could have started heparin earlier preoperatively he would probably avoid PE. On the other hand, the reason why he only had suffered minor symptom and recovered quickly could be well explained for the fact that he had preoperative administration of heparin.

Heparin exerts its anticoagulant function via catalyzing the inactivation of thrombin, factor Xa, and other clotting enzymes (15), and it is one of the commonly used anticoagulants in clinical practice as it was applied in our current randomized controlled study due to its cost advantages (16). However, heparin could also bind to cells and plasma proteins, which could lead to side effects of heparin-induced thrombocytopenia and osteoporosis (15). Thus, LMWH, which has more predictable pharmacokinetic and pharmacodynamic properties, has become more popular and replaced heparin in many clinical indications (15,17). Recent studies have compared the thromboprophylaxis efficacy of heparin with that of LMWH and found that LMWH was as effective as heparin for VTE prevention (18,19) and was even superior in PE prevention to heparin (20). However, due to longer activity duration of LMWH, there is a potential increased risk of bleeding. Therefore, the roles of heparin and LMWH playing in VTE prevention for major thoracic surgery still need to be well established.

Even though our pilot study proved that preoperative administration of heparin as thromboprophylaxis in Chinese patients intended for thoracoscopic major thoracic surgery was safe and reasonable, there are still several limitations. First, as a pilot study, a relatively small sample size could limit our analytical power. Second, due to low occurrence rate of VTE, the actual efficacy of preoperative administration of heparin needs to be validated. Finally, in our study, we only conducted this pilot study in Chinese patients, while for African and Caucasian patients, further studies are needed. Moreover, LMWH is also worthy of being studies.

Conclusions

In this pilot randomized controlled study, we explored the safety profile of preoperative administration of heparin as thromboprophylaxis in thoracoscopic major thoracic surgery in Chinese patients. Our study proved that preoperative administration of heparin was safe and reasonable in patients intended for major thoracic surgery. Our trial keeps going on, and we will present our further results in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Ethics Committee of West China Hospital, Sichuan University (approval number: 20160601) and written informed consent was obtained from all patients.

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