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Full Length Article

Fondaparinux versus nadroparin for thromboprophylaxis following minimally invasive esophagectomy: A randomized controlled trial

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ABSTRACT

Background: The methodology of thromboprophylaxis post minimally invasive esophagectomy (MIE) is unclear. Thus, we compared the efficacy and safety of fondaparinux and nadroparin on the prophylaxis of venous thromboembolism (VTE) after MIE.

Materials and methods: We conducted a randomized, double-blind, treatment-controlled study. Consecutive patients undergoing MIE randomly received a single dose of either nadroparin 2850 AxaIU (Group H) or fondaparinux 2.5 mg (Group F) daily. We used ultrasonography to identify deep vein thrombosis (DVT) on postoperative day 7. The coagulation status was examined using thromboelastography (TEG) prior to and at 0, 24, 48, and 72 h after the operation. Bleeding events were recorded during anticoagulation therapy and analysis was performed on an intention-to-treat basis.

Results: We randomly assigned the patients to Group H ($n = 57$) or Group F ($n = 59$). Symptomatic or asymptomatic DVT was identified in seven patients in Group H and one patient in Group F (12.28% vs. 1.69%, $p = 0.031$). Pulmonary embolism developed in one patient in Group H, and the VTE incidence was significantly lower in Group F than Group H (1.69% vs. 14.04%, RR: 0.121, 95% CI: 0.016–0.935, $p = 0.016$). TEG analysis showed a more inhibited coagulation profile of Group F compared with Group H reflected by the significantly prolonged R time at 48 h and 72 h after operation (6.8 ± 2.2 min vs. 8.4 ± 2.7 min, $p = 0.005$; 7.1 ± 1.6 min vs. 9.2 ± 3.7 min, $p = 0.002$). Bleeding events were not recorded in either group.

Conclusions: Fondaparinux could provide similar efficacy and safety in postoperative thromboprophylaxis following MIE compared with nadroparin.

1. Introduction

Minimally invasive esophagectomy (MIE) is being increasingly performed in esophageal cancer patients in the last decade [1–3] as the operative wound is reduced using this technology. However, the use of artificial pneumothorax and pneumoperitoneum during MIE impedes venous return and blood flow leading to increased intrapleural and intra-abdominal pressure. This could potentially lead to lethal complications, including venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE) [4–6]. Activation of platelet coagulation cascades, overproduction of procoagulant components due to tumor and surgery, and prolonged operation time [7–15] also predispose patients undergoing MIE to postoperative VTE [16,17]. Although a previous study reported the incidence of DVT, PE, and VTE as 6.1%, 2.4%, and 7.3% within 1 month after esophagectomy [18], thromboprophylaxis recommendations are rare among these patients. The American College of Chest Physicians (ACCP) guidelines recommend esophagectomy followed by thromboprophylaxis with low-molecular-weight heparin (LMWH) [11], but the optimal timing and dosage are unclear among patients undergoing MIE. In clinical work, VTE chemoprophylaxis widely varies in drug choice, dosage, and duration [19], and fatality is unavoidable even after the preventive use of LMWH after surgery [20].

Fondaparinux is a synthetic anticoagulant recommended as an alternative to LMWH for postoperative thromboprophylaxis among orthopedic surgery patients [11,21–23]. However, the prophylactic use of fondaparinux in open esophagectomy or MIE patients is still unknown. We hypothesized that fondaparinux could provide an alternative to LMWH for thromboprophylaxis post MIE. To test this, we conducted a randomized controlled trial to compare the efficacy and safety of

Abbreviations: MIE, minimally invasive esophagectomy; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; ACCP, American College of Chest Physicians; LMWH, low-molecular-weight heparin; TEG, thromboelastography; HIT, heparin-induced thrombocytopenia

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LMWH and fondaparinux on thromboprophylaxis after MIE.

2. Material and methods

2.1. Study design

This was a prospective, randomized, double-blind, parallel-group, treatment-controlled trial conducted in the Department of Critical Care Medicine of Zhongshan Hospital, Fudan University between January 2011 and July 2012. The Ethics Committee of Zhongshan Hospital approved the protocol (No. 2010-186), and it was registered in ClinicalTrials.gov (NCT01267305). We obtained written informed consent from all participants before the surgery.

2.2. Participants

We included consecutive esophageal carcinoma patients treated with MIE and admitted to the Surgical Intensive Care Unit (SICU) after the surgery. The inclusion criteria of this study were (1) esophageal cancer patients, (2) candidates for MIE, (3) 18–75 years of age, (4) body weight > 50 Kg. The exclusion criteria were the following: (1) prothrombin time or activated partial thromboplastin time > 1.5 times the upper normal limit; (2) blood platelet count $< 50 \times 10^{12}$/L; (3) anticoagulant or antiplatelet treatment performed prior to surgery; (4) history of hemorrhagic disease; (5) history of intracranial, spinal, or ophthalmologic operation; (6) history of peptic ulcer; (7) bleeding > 400 mL intra-operation or chest drainage > 100 mL/h during the first 6 h after operation, or blood transfusion within six hours after the operation; (8) creatinine clearance < 50 mL/min or alanine transaminase > 2 times the upper normal limit.

2.3. Randomization, blinding, and interventions

Immediately after admission in SICU, the participants randomly received either subcutaneous nadroparin calcium 2850 AxaIU (Fraxiparine ®, Glaxo Smith Kline, UK, Group H) or fondaparinux sodium 2.5 mg (Arixtra ®, Glaxo Smith Kline, UK, Group F) once daily in a 1:1 ratio based on a computer-generated randomization list. We started the administration of anticoagulants 6 h after MIE [11] and continued until discharged from the hospital. The patients and investigators were blind to the grouping. In order to achieve a double-blind study, the two kinds of anticoagulants were loaded into the similar syringes before use. Anticoagulant therapy was stopped if any suspected bleeding event occurred.

2.4. Primary outcome: VTE incidence

We recorded the VTE events, including DVT and PE. An experienced sonographer performed the bedside ultrasonic examination with an ultrasound machine (Philips Ultrasound CX50, Philips Healthcare, Bothell, WA, USA) to detect lower extremity DVT immediately after admission to SICU and on the postoperative day 7. The sonographer examined the deep venous system, including common femoral vein, deep femoral vein, popliteal, anterior and posterior tibial veins. DVT was diagnosed if the image met one of the following conditions: (1) disability to demonstrate wall-to-wall apposition of the vein upon application of adequate pressure using the ultrasound transducer in the transverse plane, (2) presence of intraluminal echogenic material in sonographic imaging implying the existence of thrombus [24]. PE was suspected in patients with sudden shortness of breath, hypoxemia, or cardiac arrest, and it was confirmed using computed tomography pulmonary angiography (CTPA).

2.5. Secondary outcome: blood coagulation status measured by thromboelastography (TEG)

We measured the blood coagulation status using TEG analyzer (TEG 5000 Hemostasis analyser, Haemoscope Corporation, Niles, IL, USA) prior to surgery and at 0, 24, 48, and 72 h after operation. We recorded the following parameters: reaction time (R, min), the time elapsed from the initiation of test to the initial fibrin formation; coagulation time (K, min), the time from the beginning of a clot formation till the TEG amplitude reached 20 mm; alpha angle (α, degrees), the angle formed by the slope of a tangent line traced from the R to the K; and maximum amplitude (MA, mm), the measurement of maximal strength or stiffness of the developed clot [25,26].

2.6. Safety analysis

The main safety outcome was major bleeding which was defined as the following: (1) fatal bleeding; and/or (2) symptomatic bleeding in a critical organ such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint or intramuscular with compartment syndrome; and/or (3) extrasurgical site bleeding causing a fall in hemoglobin level ≥ 20 g/L or leading to transfusion of ≥ 2 units of whole blood or red cells with temporal association within 24–48 h to the bleeding; and/or (4) surgical site bleeding requiring a second intervention delaying mobilization or wound healing, resulting in prolonged hospitalization or a deep wound infection; and/or (5) unexpected and prolonged surgical site bleeding sufficiently large to cause hemodynamic instability and an associated fall in hemoglobin level ≥ 20 g/L, or transfusion of ≥ 2 units of whole blood or red cells with temporal association to the bleeding within 24 h [27]. Recurrent bleeding or bleeding leading to treatment discontinuation or intervention, gastrointestinal bleeding, hemoptysis, ecchymosis > 100 cm^2, epistaxis > 5 min, and spontaneous macroscopic hematuria > 24 h was defined as non-major bleeding event. Minor bleeding was defined as any other overt bleeding [28]. We recorded all the bleeding events during the treatment, and the prophylaxis therapy was stopped in the event of any suspected major, non-major, or minor bleeding event. The volume of chest drainage and hemoglobin concentration was recorded daily after the surgery for three days.

2.7. Statistical analysis

We calculated the sample size according to Rollins's study [4] where the postoperative incidence of VTE in esophageal cancer patients was reported to be 7% and Turpie's meta-analysis [29] where fondaparinux achieved 50% risk reduction of VTE compared with LMWH. We took a sample size of 55 patients in each group which provided a statistical power of 80%, a two-sided type I error rate of 5%, and a dropout rate of 10%. Finally, we expanded the sample size to 60 patients per group to increase the validity of the study.

We performed the statistical analysis using SPSS Version 21.0 (IBM Corporation, Armonk, NY). The distribution of data was evaluated by the Shapiro-Wilks test. Continuous variables were presented as mean ± standard deviation. Student's *t*-test was used to analyze parametric continuous variables and Mann-Whitney *U* test was used to analyze nonparametric continuous variables. Categorical variables were analyzed with the χ^2 test or Fisher's exact test. All primary analyses were performed on an intention-to-treat basis. A *p*-value of < 0.05 (2-sided) was considered statistically significant.

3. Results

A total of 129 patients were enrolled from January 2011 to July 2012. Finally, 116 eligible patients were randomly assigned to Group H ($n = 57$) or Group F ($n = 59$) (Fig. 1). We recorded the baseline demographics and clinical characteristics of the patients (Table 1), and

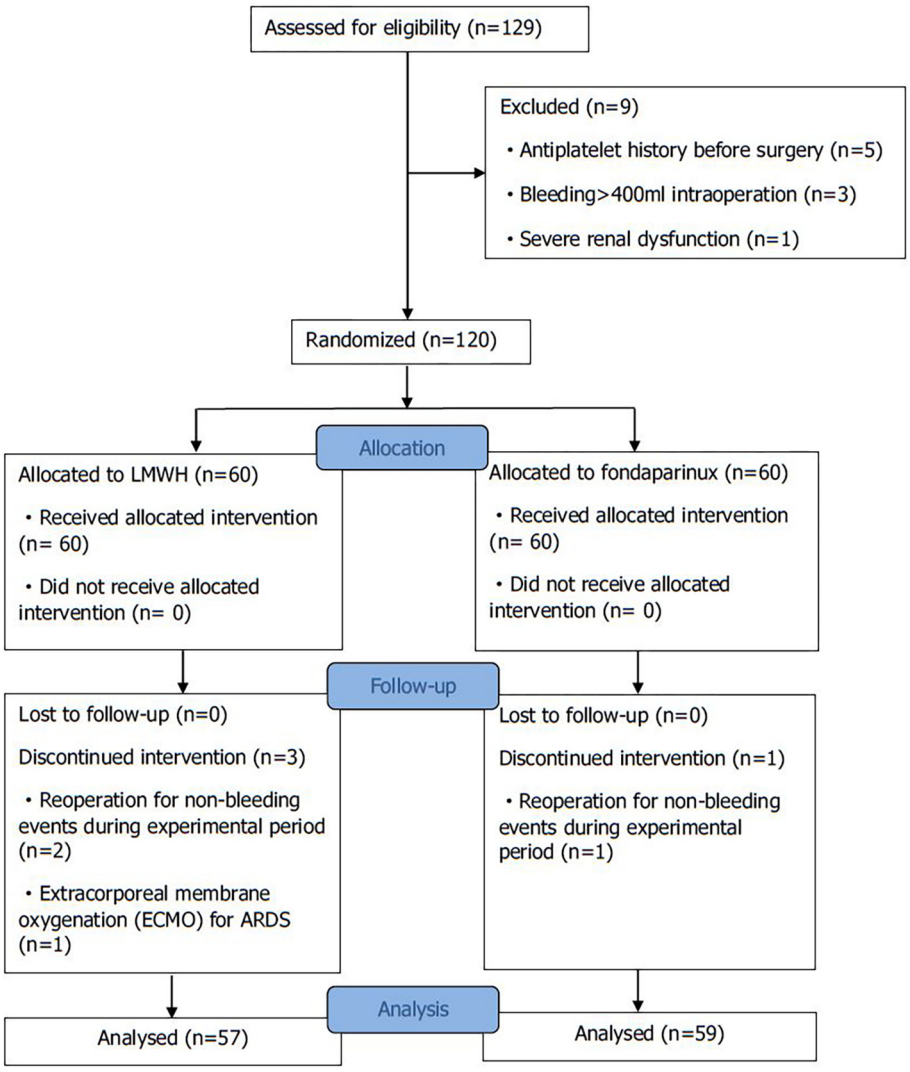

Fig. 1. Flow diagram of the trial.

there were no significant differences between the two groups.

3.1. VTE incidence

We did not detect lower extremity DVT immediately after admission to SICU. However, we observed eight DVT episodes using lower limbs ultrasound on the postoperative day 7: seven events in Group H and one event in Group F (12.28% vs. 1.69%, $p = 0.031$). No significant difference was observed in the percentage of symptomatic or asymptomatic DVT between these two groups. Symptomatic PE developed in one patient (1.75%) in Group H. The patient presented shortness of breath and hypoxemia on postoperative day 4, and we confirmed PE on the same day by CTPA. Through thrombolysis, mechanical ventilation, and symptomatic support treatment, the patient finally recovered and was discharged from hospital on the postoperative day 25. The incidence of VTE was much lower in Group F than in Group H (1.69% vs. 14.04%, RR: 0.121, 95% CI: 0.016–0.935, $p = 0.016$; Table 2).

3.2. TEG analysis

Prior to and instantly after surgery, all measured TEG values were within the normal range and comparable between Group H and Group F (Table 3). The R time was prolonged in both the groups after receiving anticoagulants, but the change was more remarkable in Group F than that in Group H at 48 h (8.4 ± 2.7 min vs. 6.8 ± 2.2 min, $p = 0.005$) and 72 h (9.2 ± 3.7 min vs. 7.1 ± 1.6 min, $p = 0.002$) after operation. After postoperative anticoagulation therapy, Group F had significantly longer K time and smaller α angle than Group H during the first three postoperative days ($p < 0.05$). MA did not differ significantly between the two groups throughout the study (Table 3, Fig. 2).

3.3. Safety analysis

All the participants completed the trial and no major, non-major, or minor bleeding events were recorded in Groups H and F throughout the study (Table 2). During the first three postoperative days, the cumulative volume of chest drainage decreased every day in both the groups. Furthermore, there were no significant differences in the chest drainage volume and hemoglobin concentration between the two groups during the first three postoperative days (Table 2). No patient died due to VTE or bleeding events during the study.

4. Discussion

We found that once daily administration of 2.5 mg fondaparinux significantly reduced the incidence of postoperative VTE following MIE compared with 2850 AxaIU nadroparin. After quantification using TEG, we found that fondaparinux significantly altered the postoperative coagulative state, which manifested as significantly prolonged R time. Bleeding events in both nadroparin and fondaparinux anticoagulation

Table 1
Patient demographics and baseline data.

Characteristics	Group H (n = 57)	Group F (n = 59)	p Value
Age (yrs)	63.1 ± 8.7	63 ± 6.5	0.966
Sex (Male, %)	30 (53)	33 (56)	0.852
BMI (kg/m^2)	21.2 ± 2.8	22.9 ± 3.9	0.143
TB (μmol/L)	10.1 ± 2.9	11.4 ± 3.8	0.265
ALT (U/L)	16.8 ± 29.9	22.4 ± 16.3	0.472
BUN (mmol/L)	5.2 ± 1.9	5.8 ± 2.4	0.380
Cr (μmol/L)	77.6 ± 20.1	79.8 ± 14.7	0.708
Hb (g/L)	131.3 ± 13.3	134.6 ± 11.8	0.413
PLT (×10^9/L)	188 ± 59	172 ± 68	0.568
Histology (n, %)			0.747
Adeno	12 (21)	16 (27)	
Squamous	44 (77)	42 (71)	
Others	1 (2)	1 (2)	
UICC stage (n, %)			0.896
0	1 (2)	1 (2)	
I	12 (21)	14 (24)	
II	19 (33)	16 (27)	
III	25 (44)	28 (47)	
G stage (n, %)			0.788
Well differentiated	5 (9)	5 (8)	
Moderated differentiated	22 (38)	21 (36)	
Poorly differentiated	30 (53)	32 (54)	
Undifferentiated	0 (0)	1 (2)	
Operation time (h)	2.8 ± 0.8	2.6 ± 0.9	0.348
Chemoradiotherapy (n, %)	10 (18)	13 (22)	0.427

ALT, alanine transaminase; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; G, grading; Hb, hemoglobin; PLT, platelets; TB, total bilirubin; UICC, Union for International Cancer Control.

Table 2
Efficacy and safety outcomes.

		Group H (n = 57)	Group F (n = 59)	p-value
VTE (n, %)		8 (14.04)	1 (1.69)	0.016
DVT (n, %)		7 (12.28)	1 (1.69)	0.031
Symptomatic DVT		2 (3.51)	0 (0)	0.239
Proximal		0 (0)	0 (0)	/
Distal		2 (3.51)	0 (0)	/
Asymptomatic DVT		5 (8.77)	1 (1.69)	0.111
Proximal		2 (3.51)	0 (0)	/
Distal		3 (5.26)	1 (1.69)	/
PE (n, %)		1 (1.75)	0 (0)	0.491
Bleeding events		0 (0)	0 (0)	1.0
major (n, %)		0 (0)	0 (0)	1.0
non-major (n, %)		0 (0)	0 (0)	1.0
minor (n, %)		0 (0)	0 (0)	1.0
Drainage volume (ml)	Day1	574 ± 273	594 ± 244	0.815
	Day2	303 ± 209	335 ± 205	0.649
	Day3	212 ± 105	224 ± 117	0.518
Hb (g/L)	Day1	128.5 ± 15.5	133.7 ± 15.2	0.301
	Day2	121.8 ± 11.0	127.8 ± 15.6	0.224
	Day3	113.9 ± 10.0	119.3 ± 14.0	0.215

VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; Hb, hemoglobin; RBC, red blood cell.

strategies were similarly low. This is the first study which compares the efficacy and safety of fondaparinux and nadroparin in postoperative thromboprophylaxis in MIE patients.

Fondaparinux and nadroparin are common and effective anticoagulants that inhibit coagulation factor Xa. A previous study showed that injection of 2.5 mg fondaparinux daily could decrease VTE by nearly half in elder patients with acute medical condition' compared with placebo [22]. A meta-analysis demonstrated that fondaparinux (2.5 mg once daily, starting at 6 h after surgery) could reduce the rate of VTE by approximately 55% without increasing the risk of clinically relevant bleeding in major orthopedic surgery compared with LMWH [21]. Another recent meta-analysis on eight RCTs with over 13,000

Table 3
Results of pre- and post-operative TEG values.

TEG values		Group H (n = 57)	Group F (n = 59)	p-value
R time (min)	Baseline	5.7 ± 0.7	5.9 ± 1.2	0.359
Normal 4–8	0h	5.1 ± 1.6	5.9 ± 2.2	0.065
	24h	7.2 ± 1.6	7.6 ± 1.7	0.314
	48h	6.8 ± 2.2	8.4 ± 2.7	0.005
	72h	7.1 ± 1.6	9.2 ± 3.7	0.002
K time (min)	Baseline	1.9 ± 0.4	2.0 ± 0.3	0.065
Normal 0–4	0h	2.4 ± 1.2	2.9 ± 1.5	0.108
	24h	2.3 ± 0.8	3.0 ± 1.1	0.004
	48h	2.1 ± 0.7	3.1 ± 1.7	0.001
	72h	2.3 ± 0.6	3.0 ± 1.5	0.010
α angle (deg)	Baseline	61.9 ± 7.3	60.8 ± 4.4	0.389
Normal 47–74	0h	58.4 ± 8.8	54.1 ± 14.6	0.116
	24h	60.9 ± 8.6	51.1 ± 9.3	0.000
	48h	64.8 ± 8.1	56.4 ± 13.9	0.002
	72h	66.1 ± 7.7	57.2 ± 12.3	0.000
MA (mm)	Baseline	63.5 ± 4.1	61.7 ± 4.6	0.082
Normal 54–72	0h	64.2 ± 9.8	62.0 ± 6.3	0.249
	24h	68.6 ± 5.7	66.8 ± 8.0	0.248
	48h	71.1 ± 6.9	67.7 ± 8.1	0.054
	72h	72.6 ± 5.7	72.3 ± 6.2	0.871

TEG, thromboelastography; K time, coagulation time; MA, maximum amplitude; R time, reaction time.

surgical or medical patients indicated that fondaparinux could reduce mortality in comparison with controls (LMWH or placebo) [30]. In our study, the incidence of VTE in Group H was significantly higher than that in Group F. Although most of the events were asymptomatic DVT, this significant difference displayed an excellent thromboprophylaxis performance of fondaparinux in esophageal cancer patients following MIE.

Upon subcutaneous injection, fondaparinux quickly reached peak plasma level and had significantly longer half-life (17 h in young subjects and 21 h in elderly volunteers [31]) and higher anti-Xa activity (700 units/mg vs. 100 units/mg) compared with LMWH. Thus, daily administration of a single dose of fondaparinux could provide similar or improved anticoagulant effect compared with nadroparin.

TEG is more sensitive and effective in monitoring the coagulation state than other traditional parameters, such as prothrombin time and activated partial thromboplastin time [26]. TEG is increasingly being used to monitor global hemostasis after surgical procedures [25,32] where the anticoagulation effect is reflected as increased R time and decreased α angle [33]. In this study, both fondaparinux and nadroparin prolonged the R time, but Group F had more pronounced changes at 48 and 72 h after the surgery. The significantly prolonged R time, which represents the time elapsed from initiation of test to the initial fibrin formation, showed stronger effect of fondaparinux to inhibit coagulation factor Xa than nadroparin. On the other hand, Group F had significantly smaller α angle after anticoagulation therapy showing reduced acceleration of fibrin build-up and cross-linking in Group F. Due to the low incidence of VTE and TEG results of Group F, we speculated that fondaparinux was at least as effective as nadroparin in preventing VTE after MIE.

The safety of fondaparinux compared with LMWH in clinical applications is still controversial [22,30,34,35]. Fondaparinux is metabolized through kidney so patients with impaired renal function, especially those with creatinine clearance < 50 mL/min need to be cautious. LMWH can inhibit coagulation factor Xa as well as IIa and may cause heparin-induced thrombocytopenia (HIT) leading to bleeding. However, due to its highly selective effect on factor Xa and no direct effect on thrombin, fondaparinux rarely causes hemorrhagic complications [31,36]. In this study, we observed no bleeding events in both the groups. Meanwhile, no significant differences existed in the chest drainage volume and the blood hemoglobin between the two groups during the first three postoperative days. All these results

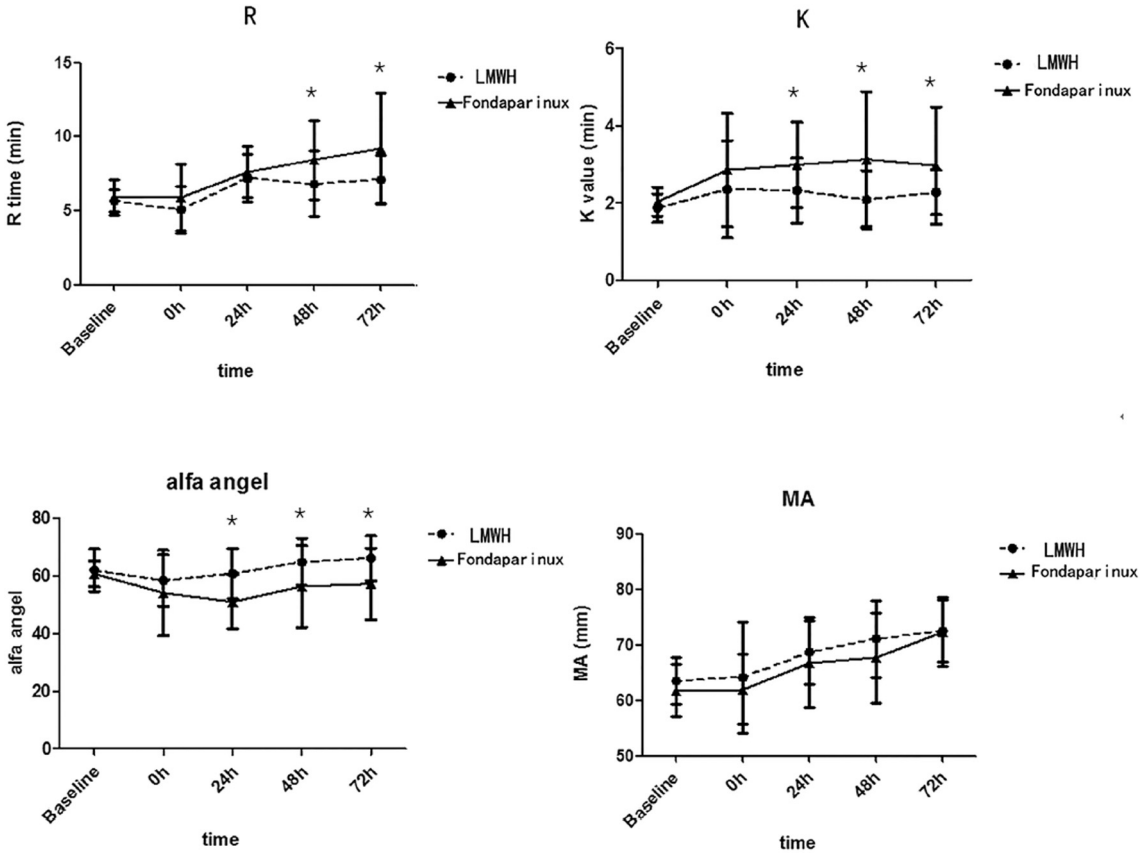

Fig. 2. TEG measures in the two groups. TEG parameters, including reaction time (R), coagulation time (K), alpha angle, and maximum amplitude (MA) were recorded prior to and at 0, 24, 48, and 72 h after operation. *, $p < 0.05$.

demonstrate that fondaparinux does not increase the risk of postoperative bleeding and is equally safe as nadroparin.

Our study had several potential limitations. First, it was a single center trial with limited number of participants. Secondly, although upper extremity deep vein thrombosis accounted for 4% to 10% of DVT cases [37], we did not take this kind of DVT into account in our study. Third, most of the DVT events were asymptomatic, and the ultrasonic examination could provide false negatives in the DVT diagnosis influencing the results. Thus, we need to interpret the results carefully and further validate them in well-designed trials with more subjects.

In conclusion, administration of single dose of 2.5 mg fondaparinux daily provides similar efficacy and safety in the postoperative prophylaxis of VTE in esophageal cancer patients following MIE compared with 2850 AxaIU nadroparin. Fondaparinux also significantly prolongs R time, K time, and decreases α angle compared with nadroparin. Thus, fondaparinux could be a promising option for thromboprophylaxis in thoracic surgery patients.

Trial registry

ClinicalTrials.gov; No: NCT01267305

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Conflicts of interest

The authors have no competing interests to declare.

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