

## Original Article

# Relevance of anticoagulation time window in preventing postoperative venous thromboembolisms (VTE) after spinal surgery

Wei Du<sup>1</sup>, Chunhong Zhao<sup>2</sup>, Jingjie Wang<sup>1</sup>, Yan Ding<sup>1</sup>, Jianfeng Zhang<sup>1</sup>, Shuqin Ni<sup>1</sup>, Jianqing Liu<sup>1</sup>, Binghua Shen<sup>1</sup>

Departments of <sup>1</sup>Spine Surgery, <sup>2</sup>Hematology, Yantai Shan Hospital, Yantai 264001, Shandong, China

Received August 7, 2018; Accepted November 8, 2018; Epub March 15, 2019; Published March 30, 2019

**Abstract:** The present study aimed to examine the anticoagulation time window in preventing postoperative venous thromboembolisms (VTE) after spinal surgery. Patients were randomly divided into 3 groups, according to venous thromboembolism risk indexing (low-risk group, middle-risk group, high-risk group, extremely high-risk group, middle-risk group, high-risk group, and extremely high-risk group). In the A group, anticoagulation was performed at 24 hours after surgery. In the B group, anticoagulation was performed at 48 hours after surgery. In the C group, anticoagulation was performed at 72 hours after surgery. According to incidence of VTE (end of efficacy) and rate of bleeding (safe endpoint), appropriate anticoagulation time windows were developed for each VTE risk group. Thrombotic events and bleeding events were simultaneously recorded. For the 253 patients in the middle-risk group, 6 thrombotic events were detected (2.37%). A total of 12 were detected (3.75%) for the 320 patients in the high-risk group. A total of 25 were detected for the extremely high-risk group (9.09%). Regarding safety end results, 15 patients had bleeding events (5.93%) in the middle-risk group, 15 had bleeding events (5.31%) in the high-risk group, and 13 had bleeding events in the extremely high-risk group (4.66%). VTE incidence rates can be reduced by selecting adaptive time windows to perform anticoagulant therapy based on VTE risk indexing, ensuring anticoagulation efficacy and reducing incidence of bleeding. Therefore, anticoagulant therapy should be performed at 24 hours in extremely high-risk groups after spinal surgery, 48 hours in high-risk groups, and 72 hours in middle-risk groups. This treatment can effectively reduce the occurrence of thrombotic events, especially severe venous thromboembolisms, without increasing the risk of bleeding.

**Keywords:** Anticoagulation, time window, venous thromboembolism (VTE)

## Introduction

With the development of spinal surgery techniques, occurrence rates of postoperative venous thromboembolisms (VTE), including DVT (deep venous thrombosis of the lower extremities) and PE (pulmonary embolism), have gradually improved to 0.3-31% [1-4]. Although there is controversy concerning the necessity of routine use of anticoagulants after spinal surgery to prevent thrombosis, most reports have suggested that proper anticoagulant drugs can reduce incidence of postoperative thrombosis in vertebral high-risk patients with spinal disorders, especially spinal cord injuries and spinal tumors [5-7]. Spinal surgeons do not accept anticoagulant drugs. One

of the main reasons is the increased potential bleeding risk introduced by anticoagulant drugs, such as wound bleeding and spinal hematoma formation. Due to the specificity of spinal surgeries, once an intraspinal hematoma is detected that is difficult to absorb after surgery, it will undoubtedly increase the risk of secondary spinal cord and nerve injuries. Based on the potential risk of anticoagulant drugs, spinal surgeons must balance gains and losses in preventing thrombosis and potential bleeding. Warwic believed that the key is the right timing of anticoagulant drugs [8]. A surgical area within 24 to 48 hours after surgery has a higher risk of bleeding, thus anticoagulant drugs should be carefully used. Regarding the starting point for anticoagulant therapy after surgery, Glotzbecker

# Anticoagulation time window in preventing postoperative VTE

**Table 1.** Venous thromboembolic risk indexing for orthopedic surgery

Risk indexing	Judgment indicators
Low risk	Operation time < 45 min, age < 40 years old, no risk factors existed Operation time < 45 min, age 40-60 years old, no risk factors existed
Middle risk	Operation time < 45 min, risk factors existed Operation time > 45 min, age < 40 years old, no risk factors existed
High risk	Operation time < 45 min, age < 60 years old, risk factors existed Operation time > 45 min, age 40-60 years old, risk factors existed
Extremely high risk	Operation time > 45 min, age > 40 years old, multiple risk factors existed, such as Major orthopedic surgery, severe trauma, spinal cord injury

found that 22% of spinal surgeons recommended that anticoagulant therapy can be used for spinal cord injuries and other thrombotic high-risk patients at 48 hours after surgery, according to questionnaire survey statistics [9]. In their study, different opinions mainly included at 48 hours after surgery (15%), 72 hours after surgery (13%), 24 hours after surgery (12%), and 96 hours after surgery (10%), while some surgeons thought that prophylactic anticoagulant therapy should be started before surgery. The Chinese Medical Association formulated a guide for prevention of deep vein thrombosis of the lower extremities after major orthopedic surgery in 2009. However, it is more suited to artificial total hip arthroplasty, total knee arthroplasty, and hip fracture prevention. The 8th ACCP Conference recommends that prophylactic antithrombotic measures can be not used after elective degenerative spinal surgery and it is necessary that precautionary measures are only for those with high-risk diseases, such as spinal cord injuries, old age, and history of prior thrombosis [10, 11]. However, the North American Spine Society recommends that all physical surgical interventions should be taken after spinal surgery to reduce incidence of thrombotic events, suggesting that combined anticoagulant therapy should be used for paraplegia, anterior, and posterior joint surgery, as well as other high-risk cases [12].

Due to the specialty of spine surgeries, there are no unified and authoritative guidelines concerning postoperative anticoagulants and antithrombotic treatment procedures. Although some reports have shown that very low incidence of deep vein thrombosis and pulmonary embolism were found after routine spinal surgery, some high-risk cases, such as spinal cord injuries and spinal tumors, may have higher

lower extremity deep vein thrombosis incidence, even fatal pulmonary embolisms. Indeed, spinal surgeons should carefully choose the optimum measure, balancing the pros and cons of anticoagulation to prevent bleeding. However, few studies have investigated the optimal time window of anticoagulation in spinal surgery.

The present experiment was designed to study different VTE risk postoperative anticoagulation time windows for spinal surgery. VTE risk indexing was used in selecting a proper time window to perform anticoagulant therapy, reducing incidence of VTE and bleeding events.

## Materials and methods

According to risk indexing in the Chinese Orthopedic Surgery Venous Thromboembolism Prevention Guidelines (Table 1), 4 groups were involved in this study: low-risk group, middle-risk group, high-risk group, and extremely high-risk group. Risk factors were mainly derived from the 8th American College of Chest Physicians Guide for the Prevention of Venous Thrombosis: age  $\geq 60$  years old, BMI  $\geq 30$  kg/m<sup>2</sup>, thrombophilia patients (such as hypertension, diabetes, hyperlipidemia, and tumors), history of previous venous thrombosis, anterior, or posterior joint surgery, spinal trauma, and spinal cord injuries. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Yantai Hospital. Written informed consent was obtained from all participants.

Participants were randomly divided into 3 groups: Group A, anticoagulation at 24 hours after surgery; Group B, anticoagulation at 48 hours after surgery; Group D, anticoagulation at 72 hours after surgery. Preventive drugs, including 40 mg low molecular weight heparin sodium

## Anticoagulation time window in preventing postoperative VTE

**Table 2.** Incidence of thrombotic events (Efficacy endpoint)

Thrombotic events	Middle risk group			High risk group			Extremely high risk group		
	24 h	48 h	72 h	24 h	48 h	72 h	24 h	48 h	72 h
Primary efficacy endpoint	0/86 (0.00%)	2/84 (2.38%)	4/83 (4.82%)	1/106 (0.94%)	4/104 (3.85%)	7/110 (6.36%)	3/89 (3.38%)	8/95 (8.42%)	14/91 (15.38%)
Death	0	0	0	0	0	1	0	1	3
Non-fatal pulmonary embolism	0	0	0	0	1	1	0	1	2
Deep vein thrombosis	0	2	4	1	3	5	3	6	9
Near end	0	0	1	0	0	2	2	4	5
Remote only	0	2	3	1	3	3	1	2	4
Severe venous thromboembolism*	0/86 (0.00%)	0/84 (0.00%)	2/83 (2.41%)	0/106 (0.00%)	1/104 (0.96%)	3/110 (2.72%)	2/89 (2.25%)	5/95 (5.26%)	7/91 (7.69%)
Symptomatic venous thromboembolism†	0/86 (0.00%)	1/84 (1.19%)	2/83 (2.41%)	0/106 (0.00%)	2/104 (1.92%)	4/110 (3.64%)	3/89 (3.37%)	6/95 (6.32%)	9/91 (9.89%)
During treatment	0	1	1	0	1	3	2	2	4
During follow-up	0	0	1	0	1	1	1	4	5

\*Indicates composite outcome of severe venous thromboembolism is formed by proximal deep vein thrombosis, non-fatal pulmonary embolism, or venous thromboembolism. †Indicates symptomatic venous thromboembolism, including any symptomatic deep venous thrombosis (proximal or distal), and non-lethal or fatal symptomatic pulmonary embolism.

**Table 3.** Incidence of bleeding (safety endpoint)

Bleeding events	Middle risk group			High risk group			Extremely high risk group		
	24 h	48 h	72 h	24 h	48 h	72 h	24 h	48 h	72 h
Any bleeding during treatment	8/86 (9.30%)	4/84 (4.67%)	3/8 (3.61%)	7/106 (6.60%)	5/104 (4.81%)	5/110 (4.55%)	5/89 (5.62%)	5/95 (5.26%)	3/91 (3.30%)
Severe bleeding	4/86 (4.65%)	0 (0.00%)	0 (0.00%)	2/106 (1.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fatal bleeding	0	0	0	0	0	0	0	0	0
Inflow to vital organs	1	0	0	1	0	0	0	0	0
Hemorrhage causing reoperation	2	0	0	0	0	0	0	0	0
Surgical site bleeding	1	0	0	0	0	0	0	0	0
Causes a drop in hemoglobin	1	0	0	0	0	0	0	0	0
Causes blood transfusion ≥2 units	0	0	0	1	0	0	0	0	0
Non-severe bleeding	4/86 (4.65%)	4/84 (4.76%)	3/83 (3.61%)	5/106 (4.72%)	5/104 (4.81%)	5/110 (4.55%)	5/89 (5.62%)	5/95 (5.26%)	3/91 (3.30%)
Clinically relevant non-severe bleeding	1	1	2	1	1	0	2	2	1
Hemorrhagic wound complications	2	3	1	3	1	3	1	2	1
Other non-severe bleeding	1	0	0	2	3	2	2	1	1

## Anticoagulation time window in preventing postoperative VTE

(bought from Sanofi-Aventis company), were subcutaneously injected once daily.

Patients were observed for symptoms and signs of DVT or PE every day after surgery. They underwent color Doppler ultrasonography of the bilateral lower extremity veins once DVT or PE was detected. PE diagnosis: pulmonary angiography spiral CT examinations once PE symptoms were detected. After discharge, patients were informed about the signs and symptoms of DVT or PE. Other patients without symptoms were given lower limb deep vein ultrasound Doppler examinations at 2 days, 7 days, 14 days, and 4 weeks after surgery. DVT in any position and the number of nonfatal PE and deaths were recorded, including patients with severe and non-severe bleeding.

Efficacy endpoints mainly included composite endpoints of all deep vein thrombosis, non-fatal pulmonary embolisms, and all-cause mortality during treatment (up to 14 days postoperatively). The main secondary efficacy endpoint was severe venous thromboembolisms during treatment (until 14 days after surgery). The composite endpoint was death from proximal deep venous thrombosis, non-fatal pulmonary embolism, and venous thromboembolism. Other efficacy endpoints included symptomatic venous thromboembolisms during treatment and follow-up and death during follow-up.

The main safe end indicated severe bleeding during treatment. Severe bleeding was defined as fatal bleeding, bleeding into critical organs (such as retroperitoneal, intracranial, intraocular, intraspinal), reoperation caused by bleeding, obvious bleeding with hemoglobin drop  $\geq 20$  g/L outside the surgical site in clinic (the first day after surgery was the reference value), or the need to input  $\geq 2$  units of whole blood or red blood cells. Other safe ends included all non-severe bleeding during treatment (all bleeding events not rated as severe bleeding during treatment) and hemorrhagic wound complications (composite index of wound hematoma and bleeding in surgical site).

Statistical analysis was performed using SPSS 19.0. Comparisons of distribution among efficacy endpoints and incidence of safety endpoint events were estimated using  $\chi^2$  test if sample sizes  $\geq 5$ . They were estimated using corrected  $\chi^2$  test if sample sizes were less than 5

and larger than 1 or using Fisher's exact test.  $P < 0.05$  indicates statistical difference.

### Results

#### *Efficacy endpoints*

In the middle-risk group ( $n = 253$ ), 6 patients were detected with thrombotic events (2.37%). In the 48 hours group ( $n = 2$ , 2.38%), 2 patients were detected with posterior tibial vein embolization, 1 patient felt calf swelling and discomfort, and 1 did not show any symptoms (**Table 2**). In the 48 hour group, 1 case showed external iliac vein embolization, with lower limb swelling and pain, 1 case was detected with femoral vein embolisms and lower limb swelling and pain, 1 case was detected with posterior tibial vein embolization with calf pain, and 1 case was found with femoral vein embolisms with lower limb swelling during the follow-up period (**Table 2**).

In the high-risk group ( $n = 320$ ), 12 patients had thrombotic events (3.75%). Of these, 1 patient was found in the 24-hour group (0.94%) with axillary vein embolisms. A total of 4 patients were found in the 48-hour group (3.85%), including 1 case with external iliac vein embolization, lower limb swelling, difficulties in breathing, progressive decrease in arterial oxygen tension, and pulmonary artery CTA confirmed left upper lobar artery embolisms. A total of 3 patients showed posterior tibial vein embolization, while 2 patients felt calf swelling and discomfort. In the 72-hour group (6.36%), 1 patient died due to pulmonary embolism on the 7<sup>th</sup> day after surgery (with external iliac vein and femoral vein embolisms), 1 patient died due to non-fatal pulmonary embolisms, 1 case was found with posterior tibial vein embolization with calf pain, 1 case was found with femoral vein embolism during the follow-up period with lower limb swelling, and 1 case was found with femoral vein embolisms with lower limb swelling (**Table 2**).

In the extremely high-risk group ( $n = 25$ , 9.09%), in the 24-hour subgroup, 1 case was detected with femoral vein embolisms with thrombosis floating and swelling of lower limbs, 1 case was detected with external iliac vein embolization with lower limb swelling, and 1 case was found with axillary vein embolisms. In the 48-hour group ( $n = 8$ , 8.42%), 1 case was detected with

## Anticoagulation time window in preventing postoperative VTE

**Table 4.** Incidence of thrombotic events among each risk group

		Among middle	Among high	Among extremely
		risk group	risk group	high risk group
		<i>P</i> value	<i>P</i> value	<i>P</i> value
Primary efficacy endpoint	24 h vs 48 h	0.151#	0.168*	0.148*
	48 h vs 72 h	0.391*	0.404*	0.142
	72 h vs 24 h	0.039#	0.035*	0.006*
Primary secondary efficacy endpoint (Severe venous thromboembolism)	24 h vs 48 h	1#	0.311#	0.285*
	48 h vs 72 h	0.153#	0.34*	0.5
	72 h vs 24 h	0.147#	0.047#	0.039*
Other efficacy endpoints (Symptomatic venous thromboembolism)	24 h vs 48 h	0.311#	0.151#	0.354*
	48 h vs 72 h	0.551*	0.448*	0.371
	72 h vs 24 h	0.147#	0.048#	0.039*

\*Indicates statistical analysis using corrected  $\chi^2$  test; #Indicates statistical analysis using Fisher's exact test.

axillary vein embolisms, 4 cases were detected with femoral vein embolisms with lower limb swelling and pain, 1 case was found with presacral venous embolization, 1 patient died due to pulmonary embolism on the 7<sup>th</sup> day after surgery, and 1 patient died due to non-fatal pulmonary embolisms. In the 72-hour group ( $n = 14$ , 15.38%), 2 patients died due to pulmonary embolisms on the 10<sup>th</sup> day after surgery, 1 patient died on the 13<sup>th</sup> day, 2 patients died due to non-fatal pulmonary embolisms, 2 patients were detected with axillary vein embolisms, 2 cases were found with femoral vein embolisms during follow-up, and 3 patients were found with posterior tibial vein embolization with lower limb swelling and pain.

### Safety endpoints

Of the 253 cases in the middle-risk group, 15 had bleeding events (5.93%). Eight cases were found in the 24-hour group (9.30%), including 4 with severe bleeding, 2 cases needed reoperations because of neurological dysfunction due to epidural hematoma on days 1 and 2 after surgery, and 1 patient was found with severe headaches caused by intracranial hemorrhage on day 4 after surgery. Symptoms were improved by dehydration, swelling, and neurotropholy treatments. One patient was suspected to have gastrointestinal bleeding (vomiting, bloody diarrhea) with low hemoglobin (8 g/L), 4 patients were identified as non-severe bleeding, 3 patients were blade bleeding (one was infected), and 1 patient was suspected to have gastrointestinal bleeding events and fecal occult blood positive (**Table 3**).

In the 48-hour group, there were 4 patients (4.67%), including 4 patients with non-severe

bleeding, 1 patient with spontaneous hematoma outside the blade, 1 patient with large area subcutaneous freckle, and 2 patients with blade bleeding. There were 3 patients in the 72-hour group, mainly including 3 patients with non-severe bleeding, 1 patient with spontaneous hematoma outside the blade, and 2 patients with blade bleeding (**Table 3**).

In the high-risk group, there were 17 cases (5.31%). In the 24-hour subgroup ( $n = 7$ , 6.60%), there were 2 patients with severe bleeding and 5 patients with non-severe bleeding. In the 48-hour group, 5 patients (4.81%) were identified with non-severe bleeding. A total of 5 patients (4.55%) in the 72-hour group were found with non-severe bleeding.

In the extremely high-risk group, there were 13 patients with bleeding events (4.66%). In the 24-hour group (5.62%) and 48-hour group (5.26%), 5 patients were found with non-severe bleeding, respectively, while 3 patients were identified in the 72-hour group (4.55%) with non-severe bleeding.

### Incidence of thrombotic events

No significant differences in primary efficacy endpoints were detected between 24-hour and 48-hour groups and 72-hour groups ( $P > 0.05$ ), while significant differences could be found between 24-hour and 72-hour groups ( $P = 0.039$ , 0.035, 0.006, respectively, **Table 4**). Regarding primary secondary efficacy endpoints (severe venous thromboembolism), significant differences were found between 24-hour and 72-hour groups in the high-risk group and extremely high-risk group ( $P < 0.05$ ). For other efficacy endpoints (symptomatic ven-

## Anticoagulation time window in preventing postoperative VTE

**Table 5.** Incidence of bleeding events within each risk group

		Comparison among middle risk groups <i>P</i> value	Comparison among high risk groups <i>P</i> value	Comparison among extremely high risk groups <i>P</i> value
Any bleeding during treatment	24 h vs 48 h	0.247*	0.575	0.916
	48 h vs 72 h	0.711*	0.927	0.508*
	72 h vs 24 h	0.134*	0.509	0.45*
Severe bleeding	24 h vs 48 h	0.045#	0.159#	1#
	48 h vs 72 h	1#	1#	1#
	72 h vs 24 h	0.047#	0.148#	1#
Non-severe bleeding	24 h vs 48 h	0.972*	0.975	0.916
	48 h vs 72 h	0.711*	0.952	0.508*
	72 h vs 24 h	0.735*	0.927	0.45*

\*Indicates statistical analysis using Corrected  $\chi^2$  test; #Indicates statistical analysis using Fisher's exact test.

ous thromboembolism), significant differences were found between 24-hour and 72-hour groups in the high-risk group and extremely high-risk group ( $P < 0.05$ , **Table 4**).

### *Incidence of bleeding*

No significant differences were found in any bleeding events and non-severe bleeding events during the treatment process ( $P > 0.05$ , **Table 5**), but significant differences were found in severe bleeding between 24-hour and 48-hour groups ( $P = 0.045$ ) in the middle-risk group and between 24-hour and 72-hour groups ( $P = 0.047$ , **Table 5**).

### **Discussion**

Although the necessity of conventional anticoagulants after spinal surgery to prevent thrombosis remains highly controversial in academic circles, most studies suggest that proper anticoagulant drugs can reduce the incidence of postoperative thrombosis in the spine, particularly in high-risk cases, such as spinal cord injuries and spinal tumors [3, 4, 13, 14]. The main shortcoming of anticoagulants is the potential increased risk of bleeding, such as wound bleeding and spinal hematomas [15]. Due to the specialty of spine surgeries, intraspinal hematoma will increase the risk of secondary spinal cord and nerve injuries [6, 7, 16]. Based on these potential risks, spinal surgeons must weigh the pros and cons in preventing thrombosis and potential bleeding. The most serious complication related to drug anticoagulation is spinal epidural hematoma and its neurological sequelae (incidence is 0.1-0.7%) [17-19]. However, these complications may also occur in the

absence of anticoagulant drugs. Despite drugs that prevent and control VTE increasing the risk of spinal epidural hematomas, it is difficult to determine which patients are more likely to have this complication due to less data. Kou et al. proposed that only when patients have multiple steps of coagulation dysfunction will they be at a high-risk state of spinal epidural hematomas. They used logistic regression analysis to assess risk factors [10]. Gerlach et al. pointed out about 77% show new neurological impairment [17, 20], with early surgical decompression as the best solution for nerve function recovery. Patients undergoing surgical decompression within 8 hours of symptom onset can recover all or part of their neurological function [21], while 60% of patients undergoing early surgical decompression have complete recovery of neurological function after surgery [17]. Postoperative bleeding in patients with spinal cord injuries has been related to the use of anticoagulant drugs. Bleeding from the upper gastrointestinal tract and surgical site account for 16% and 19% of bleeding complications, respectively [22, 23]. However, there are no reports concerning epidural hematomas.

Doctors should pay attention to whether these patients tend to bleed. Once the diagnosis of epidural hematoma is confirmed, surgical decompression is more beneficial to recovery of nerve function. Intraspinal hematomas after surgery will increase the risk of secondary spinal cord and nerve injuries, especially in the cervical and thoracic vertebrae, further increasing the risk of secondary nerve injuries. Warwic believed that the key lies in the right timing of anticoagulant drugs, suggesting that 24-48

## Anticoagulation time window in preventing postoperative VTE

hour groups should use anticoagulant drugs with caution due to high risk of bleeding [8]. Due to the characteristics of spinal surgery, uniform and authoritative guidelines for postoperative anticoagulation and antithrombotic treatment procedures are not yet available. Deciding which measures are best and how to weigh the pros and cons of anticoagulation and prevention of bleeding requires that spinal surgeons be cautious in their clinical work. Thus, the present study was designed to examine postoperative anticoagulation time windows for spinal surgery after different VTE risks. Selection of an appropriate time window for anticoagulant therapy based on VTE risk scores can reduce incidence of VTE and reduce incidence of bleeding events.

The present study found that significant differences in incidence of thrombotic events was found between 24-hour and 72-hour groups ( $P < 0.05$ , **Table 4**), indicating that anticoagulation can significantly reduce incidence of thrombotic events at 24 hours after the operation. In high-risk and extremely high-risk groups, severe venous thromboembolisms and symptomatic venous thromboembolisms indicated significant differences between 24-hour and 72-hour groups ( $P < 0.05$ ), implying that anticoagulation at 24 hours after surgery can greatly reduce the occurrence of severe venous thrombosis and symptomatic venous thromboembolisms. Moreover, any bleeding, severe bleeding, and non-severe bleeding during treatment showed no significant differences between different time points in high-risk and extremely high-risk groups ( $P > 0.05$ , **Table 5**). Therefore, it is recommended that anticoagulation should be performed at 24 hours after surgery in high-risk groups, effectively reducing occurrence of thrombotic events, especially severe venous thromboembolisms, without increasing the risk of bleeding. In the high-risk group, although no significant differences were found between 24-hour and 48-hour, as well as 24-hour and 72-hour groups ( $P > 0.05$ , **Table 3**), non-severe bleeding knife-edge related complications were detected in 4 patients. One was infected. Thus, anticoagulation at 24 hours may increase wound complications. More importantly, main efficacy end points, severe venous thromboembolisms, and symptomatic venous thromboembolisms in the high-risk group revealed no dif-

ferences between 24-hour and 48-hour groups ( $P > 0.05$ , **Table 4**), indicating that anticoagulation should be performed at 48 hours in high-risk groups. In the middle-risk group, primary efficacy endpoints showed significant differences between 24-hour and 72-hour groups ( $P < 0.05$ , **Table 4**), suggesting that anticoagulation can significantly reduce thrombotic events at 24 hours after the operation. However, severe bleeding events showed differences between 24-hour and 48-hour groups, as well as 24-hour and 72-hour groups ( $P < 0.05$ , **Table 5**), indicating that anticoagulation at 24 hours after surgery in moderate-risk patients significantly increased bleeding risk, compared with anticoagulation at 48 hours and 72 hours. Further statistical analysis revealed no significant differences between different groups ( $P > 0.05$ , **Table 5**). However, 6 patients increased the possibility of blade complications at 48 hours. Thus, it is recommended that anticoagulation should be performed at 72 hours after the operation in middle-risk groups.

### Limitations

The present study had several limitations. 1) This study was a single-center clinical study. A large multi-center, randomized, and double-blind clinical trial for anticoagulant therapy with a suitable time window for spinal surgery could increase the level of credible evidence for this study; 2) This study was randomly divided into anticoagulation groups at 24, 48, and 72 hours after surgery. There were no objective laboratory tests to guide anticoagulation. In recent years, the thromboelastogram has become a detection method for human blood coagulation, hemorrhages, and fibrinolytic indicators. Whether or not anticoagulation of the spine is guided by the thromboelastogram reduces incidence of VTE and reduces incidence of bleeding events; 3) Whether anticoagulant prophylaxis can be advanced or delayed, such as anticoagulation after 8 hours postoperatively or 72 hours post-requiring clinical trial confirmation.

### Conclusion

Results of the present study suggest that anticoagulant therapy should be performed at 24 hours in extremely high-risk groups after spinal surgery, 48 hours in high-risk groups, and 72

hours in middle-risk groups, effectively reducing occurrence of thrombotic events, especially severe venous thromboembolisms, without increasing the risk of bleeding.

## Acknowledgements

This work was supported by the Yantai Science and Technology Development Plan Project (2014WS033).

## Disclosure of conflict of interest

None.

**Address correspondence to:** Wei Du, Department of Spine Surgery, Yantaishan Hospital, No. 91 Jiefang Road Zhifu District, Yantai 264001, Shandong, China. Tel: +86 13280977560; Fax: +86 0535 6602028; E-mail: dwdoccn@163.com

## References

- [1] Cote DJ, Dubois HM, Karhade AV and Smith TR. Venous Thromboembolism in Patients Undergoing Craniotomy for Brain Tumors: A U.S. Nationwide Analysis. *Semin Thromb Hemost* 2016; 42: 870-6.
- [2] Kimmell KT and Jahromi BS. Clinical factors associated with venous thromboembolism risk in patients undergoing craniotomy. *J Neurosurg* 2015; 122: 1004-11.
- [3] Nicol M, Sun Y, Craig N and Wardlaw D. Incidence of thromboembolic complications in lumbar spinal surgery in 1,111 patients. *Eur Spine J* 2009; 18: 1548-52.
- [4] Piper K, Algattas H, DeAndrea-Lazarus IA, Kimmell KT, Li YM, Walter KA, Silberstein HJ and Vates GE. Risk factors associated with venous thromboembolism in patients undergoing spine surgery. *J Neurosurg Spine* 2017; 26: 90-96.
- [5] Lee E, Kang SB, Choi SI, Chun EJ, Kim MJ, Kim DW, Oh HK, Ihn MH, Kim JW, Bang SM, Lee JO, Kim YJ, Kim JH, Lee JS and Lee KW. Prospective study on the incidence of postoperative venous thromboembolism in Korean Patients with Colorectal Cancer. *Cancer Res Treat* 2016; 48: 978-89.
- [6] Bryson DJ, Uzoigwe CE and Braybrooke J. Thromboprophylaxis in spinal surgery: a survey. *J Orthop Surg Res* 2012; 7: 14.
- [7] Platzer P, Thalhammer G, Jaendl M, Obradovic A, Benesch T, Vecsei V and Gaebler C. Thromboembolic complications after spinal surgery in trauma patients. *Acta Orthop* 2006; 77: 755-60.
- [8] Warwick D. New concepts in orthopaedic thromboprophylaxis. *J Bone Joint Surg Br* 2004; 86: 788-92.
- [9] Glotzbecker MP, Bono CM, Harris MB, Brick G, Heary RF and Wood KB. Surgeon practices regarding postoperative thromboembolic prophylaxis after high-risk spinal surgery. *Spine (Phila Pa 1976)* 2008; 33: 2915-21.
- [10] Goldstein CL, Bains I and Hurlbert RJ. Symptomatic spinal epidural hematoma after posterior cervical surgery: incidence and risk factors. *Spine J* 2015; 15: 1179-87.
- [11] Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR and Colwell CW. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133: 381S-453S.
- [12] Schulte LM, O'Brien JR, Bean MC, Pierce TP, Yu WD and Meals C. Deep vein thrombosis and pulmonary embolism after spine surgery: incidence and patient risk factors. *Am J Orthop (Belle Mead NJ)* 2013; 42: 267-70.
- [13] Weitz JI, Middeldorp S, Geerts W and Heit JA. Thrombophilia and new anticoagulant drugs. *Hematology Am Soc Hematol Educ Program* 2004; 2004: 424-38.
- [14] Warwick D and Rosencher N. The "critical thrombosis period" in major orthopedic surgery: when to start and when to stop prophylaxis. *Clin Appl Thromb Hemost* 2010; 16: 394-405.
- [15] Acheampong P and Ford GA. Pharmacokinetics of alteplase in the treatment of ischaemic stroke. *Expert Opin Drug Metab Toxicol* 2012; 8: 271-81.
- [16] Phang I, Zoumprouli A, Saadoun S and Pappadopoulos MC. Safety profile and probe placement accuracy of intraspinal pressure monitoring for traumatic spinal cord injury: injured spinal cord pressure evaluation study. *J Neurosurg Spine* 2016; 25: 398-405.
- [17] Gerlach R, Raabe A, Beck J, Woszczyk A and Seifert V. Postoperative nadroparin administration for prophylaxis of thromboembolic events is not associated with an increased risk of hemorrhage after spinal surgery. *Eur Spine J* 2004; 13: 9-13.
- [18] Kou J, Fischgrund J, Biddinger A and Herkowitz H. Risk factors for spinal epidural hematoma after spinal surgery. *Spine (Phila Pa 1976)* 2002; 27: 1670-3.
- [19] Yi S, Yoon DH, Kim KN, Kim SH and Shin HC. Postoperative spinal epidural hematoma: risk factor and clinical outcome. *Yonsei Med J* 2006; 47: 326-32.
- [20] Agnelli G, Tonato M, Bianchini C, Amadori D, Barbui T, Cognetti F, Barni S, Labianca R, Buzzi

## Anticoagulation time window in preventing postoperative VTE

- F, Scambia G, Passalacqua R, Ricci S, Gasparini G, Lorusso V, Bonizzoni E, Tonato M; PROTECT Investigators. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol* 2009; 10: 943-9.
- [21] Vandermeulen EP, Van Aken H and Vermylen J. Anticoagulants and spinal-epidural anesthesia. *Anesth Analg* 1994; 79: 1165-77.
- [22] Eberle BM, Schnüriger B, Inaba K, Cestero R, Kobayashi L, Barmparas G, Oliver M and Demetriades D. Thromboembolic prophylaxis with low-molecular-weight heparin in patients with blunt solid abdominal organ injuries undergoing nonoperative management: current practice and outcomes. *J Trauma* 2011; 70: 141-7.
- [23] Spinal Cord Injury Thromboprophylaxis Investigators. Prevention of venous thromboembolism in the acute treatment phase after spinal cord injury: a randomized, multicenter trial comparing low-dose heparin plus intermittent pneumatic compression with enoxaparin. *J Trauma* 2003; 54: 1116-26.