The Efficacy of Early Anticoagulant Therapy for Venous Thromboembolism in Polytrauma Patients in the Acute Phase

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Objective: To determine whether antithrombotic therapy with warfarin is effective and safe in patients who developed venous thromboembolism in the acute stage of polytrauma, which is associated with bleeding risk.
Method: A retrospective study of 11 patients (8 males, 3 females; mean age, 39.8 years; injury severity score, 30.1; no fatalities) with deep venous thromboembolism and/or pulmonary embolism who were medicated with heparin and warfarin during their ICU stay.
Results: Thrombosis was diagnosed at an average of 11.8 days after admission. Thrombus formation was confirmed in pulmonary arteries in 5 cases and in deep veins in 9 cases. Diagnosis was based on Doppler ultrasound findings in 6 cases and on computed tomography findings in 5 cases. Anticoagulant therapy was used in 10 cases, but not in 1 case with cerebral contusion. Approximately 33 days after starting anticoagulant therapy, thrombi had disappeared or were reduced in size in 9 of 10 patients with no complications observed.
Conclusions: Heparin and warfarin therapy cleared deep vein and pulmonary artery thrombosis after polytrauma without any bleeding complications. Further studies are necessary to determine the safe anticoagulant dosage and duration for rapid thrombus removal.

Key words: polytrauma, venous thromboembolism, anticoagulant therapy, complication, pulmonary embolism

INTRODUCTION

Patients in a trauma intensive care unit (ICU) require prolonged bed rest and are consequently at high risk of developing deep vein thrombosis (DVT) and pulmonary thromboembolism. As pulmonary embolism (PE) is often fatal, prevention is particularly important. Pharmacological approaches and mechanical methods using compression stockings or a compression device are predominantly recommended in guidelines for thromboembolism management [1, 2].

Although the thromboprophylactic guidelines are generally effective for preventing venous thromboembolism (VTE), DVT and PE still developed in 0.7–13% of severe trauma patients who received thromboprophylaxis [3–7].

Furthermore, pharmacological thromboprophylactic measures which are recommended by the guidelines could increase the risk of bleeding in the acute stage of severe polytrauma with massive hemorrhage. Clinical application of these measures to polytrauma has not been well studied and has largely occurred on a case by case basis [8]. The critical issue is that there are no standard procedures for treating patients with severe polytrauma who develop VTE in the acute phase, despite prophylactic measures.

To safely treat polytrauma patients who develop VTE, three important questions regarding antithrombotic therapy with anticoagulants and thrombolytic agents – without increasing bleeding – must be answered. These questions are when to start therapy, which agents to use, and what dose to use. In this study, we retrospectively investigated the effects (clearance of thrombosis) and safety (without complications such as bleeding) of anticoagulant therapy using heparin and warfarin in hospitalized polytrauma patients who developed VTE in the acute stage.

PATIENTS AND METHODS

A total of 4,105 patients with severe trauma were admitted to the ICU of the emergency medical center of Tokai University Hospital between April 2006 and March 2010. Of them, 11 multiple trauma patients (8 male, 3 female; mean age: 39.8 ± 18.2 years; ISS: 30.1 ± 10.9; no fatalities) who had been diagnosed with pulmonary embolism (PE) or DVT during ICU stay were retrospectively studied.

PE and DVT were diagnosed by computed tomography (CT) and/or Doppler ultrasound. CT was routinely performed for observation of polytrauma after admission if necessary. Doppler ultrasound was performed on the lower extremities when deep venous thrombosis formation was suspected and when d-dimer was increased after admission.

The following data were collected: (1) diagnosis of thrombosis (thrombus location, cause, situation of

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diagnosis); (2) antithrombotic therapy (agent, dose, timing of therapy, use of mechanical compression, and use of inferior vena cava filter (IVCF) placement); (3) outcome of antithrombotic therapy; and (4) complications.

RESULTS

Results are summarized in the Table.

(1) Diagnosis of thrombosis

Thrombus formation was found in pulmonary arteries in 5 cases, in deep veins (from the soleus veins to the common iliac veins) in 9 cases, and in both pulmonary arteries and deep veins in 3 cases. Of the 9 cases with deep vein thrombosis, thrombus formation was present in the leg veins (soleus, popliteal, and deep femoral veins) in 4 cases, in the common iliac veins in 4 cases, and in both locations in 3 cases. One case showed thrombus formation in the pulmonary arteries, common iliac veins, and leg veins.

Thrombosis was diagnosed at an average of 11.8 ± 10.1 days (range: 3–34 days) after injury. Thrombosis was initially found when performing a Doppler ultrasound test to check for the presence of a thrombus in 6 patients who exhibited an increase in d-dimer after admission to ICU. Follow-up CT for trauma treatment revealed thrombosis in 5 cases.

(2) Antithrombotic therapy

Heparin and warfarin were used for pharmacological therapy in 10 of the 11 patients: One patient was not treated with anticoagulants due to intracranial hematoma attributed to cerebral contusion. Of the 10 patients who received anticoagulants, 9 received a combination of intravenous heparin and warfarin and 1 with hemopneumothorax, liver injury, and traumatic subarachnoid hemorrhage (patient No. 4 in the Table) received heparin only because of the high risk of intracranial hematoma enlargement. Initial administration of heparin was 5,000–10,000 U/day intravenously. However, this dose of heparin did not reduce thrombus size, so warfarin was added in doses suitable for maintaining the international normalized ratio (INR) in the target range of 2.0–3.0. The average INR during anticoagulant therapy was 1.51 ± 0.38 (range: 0.99–2.21).

Mechanical compression methods, such as using stockings or an intermittent pneumatic compression device, were used in 9 cases immediately after admission to the ICU. An IVCF was inserted in 2 patients.

(3) Outcome of antithrombotic therapy

CT and ultrasound confirmed thrombus clearance or reduction in thrombus size before hospital discharge in 9 of 10 recipients of antithrombotic treatment. The remaining patient moved to another medical institution before follow-up examination. Thrombus clearance was observed in 8 patients at an average of 32.5 ± 7.8 days after starting antithrombotic therapy. In another patient, thrombus clearance was confirmed at the outpatient clinic approximately one year later.

(4) Complications of antithrombotic therapy

No significant aggravation of bleeding was found in any of the patients who received pharmacotherapy. Enlargement of a residual frontal subcutaneous hematoma was confirmed by CT in 1 patient (patient No. 4 in the Table).

DISCUSSION

Thromboembolism prophylaxis after polytrauma includes mechanical compression methods and pharmacotherapy. Mechanical leg compression methods can be started in the acute phase of trauma immediately after hospital admission. On the other hand, practical difficulties are often encountered in the early administration of anticoagulants, such as heparin, due to the risk of re-bleeding. In this study, 9 of 11 patients started receiving mechanical compression treatment with a pneumatic compression device and compression stockings immediately after ICU admission, while none of the patients were able to receive anticoagulant therapy with heparin due to life-threatening bleeding at that time. Subsequently, PE and/or DVT were diagnosed at an average of 11.8 days after injury.

Even when thromboprophylaxis has been provided, VTE has been reported to occur in 12–13% of patients with pelvic fractures or polytrauma [4, 6]. Such patients should be proactively monitored for probable thromboembolism after ICU admission.

Color Doppler imaging is considered effective for diagnosing thrombosis of leg veins [9, 10]. We performed Doppler echograms on patients when d-dimer levels were increased after admission to the ICU or as a pre-operation work-up. Eventually, 8 patients in the present study presented with leg vein thrombosis, and mechanical methods of prophylaxis were employed after hospital admission in 6 of these patients. These findings suggest that mechanical compression methods alone are not sufficient for preventing thrombosis in leg veins.

Furthermore, PE affecting the pulmonary arteries was confirmed in 5 of our patients, 3 who presented with thrombosis of either the common iliac veins or leg veins.

Contrast-enhanced CT, which is effective for diagnosing thrombosis of the pulmonary arteries and common iliac veins, should be proactively used not only for following up trauma but also for early detection of thrombus. An IVCF was inserted in 2 of these 3 patients. When the IVCF was removed in 1 patient, clot attachment was found, suggesting that part of a peripheral clot had travelled into the filter. On the other hand, we did not find thrombosis of the common iliac veins or leg veins in 2 of the 5 PE patients.

A study on the coexistence of PE and DVT in trauma patients by Velmahos revealed that PE is not necessarily associated with DVT, suggesting the possibility of clot formation in the pulmonary arteries, which is in contrast to the commonly held theory that PE originates from DVT in the leg veins [11]. Accordingly, the mechanism of PE involving the pulmonary arteries warrants further study.

Thromboprophylaxis does not always prevent thromboembolism in the acute phase of trauma. As thrombus formation might result in PE involving the

Table Characteristics of eleven polytrauma patients with thromboembolism.

No	Age	Sex	Trauma	ISS	Day of thrombosis diagnosis	Diagnostic method	Reason for examination	Location of thrombosis			MC	Day of Anticoagulant therapy initiated		IVC filter	Treatment results
								PA	IPV	LV		Heparin	Warfarin		
1	77	F	Multiple rib fractures Hemopneumothorax Pelvic fracture Bladder injury Humerus fracture	45	Day 13	Doppler	Thrombus assessment	○		○	○	Day 15	Day25	Day18	Pulmonary thrombus disappeared 11days after treatment Venous thrombus disappeared 25days after treatment
2	47	M	Cerebral contusion Facial bone fracture	20	Day 34	CT	Respiratory failure	○			○				Not performed due to complications of hemorrhagic stroke
3	22	M	Open pelvic fracture Anorectal injury	34	Day 8	Doppler	Thrombus assessment			○	○	Day 12	Day20		Unknown due to transfer to other hospital
4	48	F	Multiple rib fractures Hemopneumothorax Liver injury Hemoperitoneum Traumatic SAH 1 & 3 Lumber transverse process fracture	22	Day 3	CT	Post-traumatic observation	○			○	Day 5			Decreased pulmonary blood clots 3days after treatment. Subcutaneous hematoma growth in the head. No intracranial hemorrhage.
5	20	M	Myocardial contusion Pulmonary contusion Liver injury Spleen injury Left femur fracture	27	Day 6	CT	Post-raumatic observation	○	○	○		Day 6	Day 13		DVT disappeared 25 days after treatment PE disappeared 25 days after treatment
6	35	M	Liver injury Concussion Right knee ligament injury	12	Day 16	CT	Post-raumatic observation	○	○		○	Day 4	Day14	Day 23	Thrombectomy on Day 23. Filter was removed after 30 days.

pulmonary arteries, and ultimately in death, thrombi must be removed. We administered heparin and warfarin in 10 of 11 cases. The remaining patient was not treated with anticoagulants due to intracranial hematoma attributed to cerebral contusion. It was reported that 3% of patients with brain trauma who received prophylaxis with low molecular-weight heparins within 48 h of hospital admission developed cerebral hemorrhage [12]. Taken together, these findings indicate that careful consideration is required before starting anticoagulant therapy in patients with brain trauma.

In this study, PE or DVT was diagnosed at an average of 12 days after injury, when patients were still at considerable risk of re-bleeding, depending on the location and severity of their injuries. For this reason, a heparin dose of 5,000–10,000 U/day, which is relatively low, was administered intravenously, and the absence of re-bleeding was confirmed by careful physical and

Table (continued) Characteristics of eleven polytrauma patients with thromboembolism.

No	Age	Sex	Trauma	ISS	Day of thrombosis diagnosis	Diagnostic method	Reason for examination	Location of thrombosis			MC	Day of Anticoagulant therapy initiated		IVC filter	Treatment results
								PA	IPV	LV		Heparin	Warfarin		
7	65	M	Hemopneumothorax Lung contusion Pancreatic injury Splenic vein and inferior mesenteric vein injury 1-3 lumber spinous process fractures	32	Day 16	Doppler	Thrombus assessment			○	○	Day 6	Day 23		Thrombus disappeared on Day 43 after treatment
8	40	M	Open pelvic fracture Urethra injury Right humerus fracture	30	Day 7	CT	Post-raumatic observation		○	○	○	Day 7	Day 9		Thrombus disappeared 1 year after treatment at outpatient clinic
9	32	M	Hemopneumothorax Open pelvic fracture Splenic injury DBI Right femur fracture	50	Day 19	Doppeler	Thrombus assessment			○	○	Day 22	Day 22		Thrombus disappeared 34 days after treatment
10	25	M	Facial bone fracture Open fracture of right leg	25	Day 11	Doppler	Infection focus assessment			○	○	Day 11	Day 11		Thrombus disappeared 20days after treatment
11	27	F	Orbital fracture Hemopneumothorax Pulmonary contusion 3 thoracic spine compression fracture Tibiofiblar open fracture	34	Day 9	Doppler	Thrombus Assessment		○	○		Day 9	Day 28		Thrombus disappeared 39 days after treatment

ISS: Injury severity score, PA: pulmonary artery, IPV: Intrapelvic vein, LV: Leg vein, MC: Mechanical compression, IVC: Inferior vena cava, SAH: Subarachnoid hemorrhage, DBI: Diffuse brain injury

CT examination before starting the administration of warfarin.

Warfarin should be administered at doses that maintain the INR in the target range of 2.0–3.0 for thromboprophylaxis [13]. We determined warfarin dose on the basis of the results of INR monitoring for the treatment of thromboembolism. Actual daily doses of warfarin were 1–6 mg, depending on the daily needs of individual patients. The average INR during warfarin therapy in 9 cases was 1.57 ± 0.35, which was lower than the expected target range.

We employed CT and Doppler ultrasound to examine changes in thrombus size in 9 patients who were receiving heparin and/or warfarin therapy. Thrombus clearance or reduction in thrombus size was confirmed in all 9 patients approximately one month after starting therapy. One patient showed only reduction in thrombus size at hospital discharge, but thrombus clearance was confirmed on outpatient examination approximately one year later.

Despite our concerns, bleeding complications and consequent shock during anticoagulant therapy were absent. Warfarin is an anticoagulant − not a thrombolytic agent. A possible mechanism for thrombus clearance, as observed in this study, is the involvement of endogenous fibrinolysis while warfarin prevents new thrombus formation and growth. Although the INR in this study (1.57 ± 0.35) was lower than the INR target (2.0), it might be a safe enough level that is not associated with re-bleeding risk during the acute stage of polytrauma, and at the same time, an effective enough level to reduce thrombus size. Considering that fibrolytic therapy such as that with urokinase and tissue plasminogen activator potentially causes re-bleeding if used during the acute phase of polytrauma, anticoagulant therapy such as that with warfarin is likely to be safer. However, one month is needed before thrombus removal. It is necessary, therefore, to identify the INR level that corresponds to faster and safer thrombolysis by using a larger study population.

Although pharmacological anticoagulant therapy should be continued for 3 months [14, 15], we withdrew warfarin treatment as soon as thrombus removal was confirmed and patients had regained mobility. Similar to INR, the duration of anticoagulant therapy should also be investigated by using a larger study population.

Despite following the guideline for thromboprophylaxis, cases of thromboembolism remain to some extent during the acute phase of polytrauma. A standard procedure is required for treating trauma patients who develop VTE in the acute phase despite prophylactic measures. Even though the number of the patients at present is still small, anticoagulant therapy with heparin and warfarin − and without re-bleeding − might prove effective. Safe anticoagulant doses and the duration of therapy that achieves thrombus clearance, as well as associated indexes, need to be determined in future investigations.

LIMITATIONS

This is a retrospective study with a relatively small number of patients (n = 11). This small sample size may have been due to a low diagnostic rate of DVT at our facility, largely because we have not yet established a diagnostic protocol for DVT in the acute phase of trauma.

We perform contrast-enhanced thoracoabdominal CT relatively routinely for post-traumatic observation. However, lower-extremity Doppler ultrasound is used to scan patients with recurrent d-dimer elevation and is thus not performed in all patients. In addition, Doppler ultrasound procedures and analysis are complex to perform. For these reasons, lower-extremity Doppler ultrasound is performed infrequently in the diagnosis of lower-extremity DVT, resulting in a relatively small number of cases with acute post-traumatic DVT.

To increase the number of cases, we plan to develop an appropriate diagnostic protocol for DVT and PE in the acute post-traumatic phase and perform Doppler ultrasound as routinely as thoracoabdominal CT.

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