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ORIGINAL RESEARCH

Laboratory markers and risk of secondary hemorrhagic complications after anticoagulation due to venous thromboembolism in the early postoperative phase after neurosurgical procedures

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Abstract

Deep venous thromboses (DVT) and venous thromboembolisms (VTE) are serious complications after neurosurgical procedures. Hemorrhagic complications of therapeutic anticoagulation on the other hand are also highly dreaded due to the high risk of permanent neurological deficit. Clear guidelines concerning dosage and duration of anticoagulation still do not exist for neurosurgical practice. Over a 10-year episode, patients with postoperative DVT or VTE were retrospectively identified and demographic risk factors as well as routine laboratory coagulation parameters were assessed. The goal was to determine patients at risk for a severe course of thrombosis and complications due to anticoagulation. In total, 173 patients with DVT or VTE were identified. Clinical effect of thrombosis was severe in 32.4% and fatal in 5.8% of all patients. Spinal surgery was associated with a higher risk of major or fatal outcome of thrombosis as compared to cranial procedures (fatal: 12.1 *vs.* 4.3%, $p = 0.035$). Elevated partial thromboplastin time, low platelet levels and low quick on diagnosis of thrombosis were associated with a fatal clinical course ($p = 0.02$, 0.04 and 0.02 respectively). Severe hemorrhagic complications on the other hand occurred in 6.6%, 0.6% were fatal. D-dimer did not predict the course of DVT/VTE but higher levels of D-dimer on day 3 after diagnosis of DVT/VTE were associated with a higher risk of severe bleeding complications (cutoff 4.95 μg/mL). Partial thromboplastin time after initiation of anticoagulation was not associated with hemorrhagic complications and might thus be not helpful to determine the risk of bleeding complications during the early postoperative phase. D-dimer might be of additional use to detect early bleeding complications.

Keywords

Deep venous thrombosis; Pulmonary embolism; Neurosurgery; D-dimer; Laboratory marker

1. Introduction

Deep venous thromboses (DVT) and venous thromboembolisms (VTE) are serious complications after neurosurgical procedures. Following electric brain tumor surgery, an incidence of 5.5–13.7% has been reported [1]. A large descriptive cohort study with more than 1000 patients, reports on pulmonary artery embolisms (PE) with an incidence of 3.3% [2]. Postoperative preventive anticoagulation treatment with low molecular weight or unfractionated heparin has been associated with a significantly lower incidence of thromboembolic events. A large investigation of VTE after craniotomy for malignant brain tumors revealed incidence of 2.6% and 1.5% for DVT and PE, respectively. Age and body-mass-index were predictors of VTE as well as longer duration of surgery and neurological status [3].

An excellent screening tool for VTE are D-dimer, the degradation products of fibrinolysis. They consist of covalently conjugated fibrin-fragments. For the detection of DVT, D-dimer show a high sensitivity (95.7%) but low specificity (40.0%) [4]. Negative D-dimer-testing can reliably rule out venous thrombosis, especially in the outpatient setting [5]. Postoperative application of low-molecular weight heparin reduces the incidence of venous thrombosis after spinal surgery and concomitantly leads to lower D-dimer-levels [6]. In neurosurgical patients after spinal surgery, D-dimer levels higher than 2.1 mg/dL on the 3rd postoperative day are associated with DVT with a sensitivity of 100% and a specificity of 81% [7, 8]. For patients after craniotomy, a cut-off of 2.0 mg/dL was postulated with a sensitivity of 95% [9].

Hemorrhagic complications have been found to be more frequent in patients receiving heparin after brain surgery with an incidence of 2.3% as compared to 1.4% [3]. Significant bleeding due to therapeutic anticoagulation after the detection of a DVT has been reported with an incidence of about 4% in patients with or without prior surgery [10]. However, little is known about the risks in neurosurgical patients with DVT or VTE in the early postoperative phase. Even minor hemorrhagic complications are highly dreaded due to the high risk of permanent neurological deficits after intracranial or intraspinal bleeding. Also, clear guidelines concerning dosage and duration of anticoagulation therapy do not exist for neurosurgical practice [11]. Both, under and overtreatment of thromboembolic complications are therefore possible threats that must be faced in everyday practice.

Evidence in favor of routine-D-dimer-monitoring for therapeutic anticoagulation is sparse [12], but has been shown to play an important role in predicting recurrent thrombosis [13]. In our institution, D-dimer monitoring is routinely applied in patients diagnosed with a DVT or VTE. The aim of this study was to investigate the role of routine activated partial thromboplastin time (pTT) and D-dimer monitoring during anticoagulation therapy and its association with the further clinical course and bleeding complications. Secondly, we assessed risk factors and the association of laboratory parameters with the clinical outcome in neurosurgical patients.

2. Methods and materials

A retrospective descriptive study was performed evaluating patients between 2008 to 2017 in a single academic tertiary care neurosurgical center. All patients treated at our institution who underwent a neurosurgical procedure requiring inpatient treatment and with a postoperative diagnosis of DVT or VTE were included.

The primary aims were to evaluate the incidence of symptomatic DVT and VTE after neurosurgical interventions as well as bleeding complications after anticoagulation. In addition, demographic details, postoperative laboratory parameters and their association with thrombosis as well as the effect of anticoagulation on pTT and D-dimer-levels as a monitoring tool were explored.

Cases of DVT and VTE were identified via analysis of ICD codes (DRG I26, I60, I80). Data acquisition was performed via investigation of radiological and laboratory results as well as Intensive Care Unit (ICU) charts and discharge reports.

Laboratory data was collected on the day of surgery and on days 1, 3, 5 and 7 (= pod 0, 1, 3, 5, 7 respectively) as well as on the day of diagnosis and on days 1, 3, 5 and 7 (= pdd 0, 1, 3, 5, 7 respectively) and on the day of a bleeding complication, if applicable, and on days 1, 3, 5 and 7 (= pcd 0, 1, 3, 5, 7 respectively). We evaluated pTT (coagulometric turbidimetry (second), normal value <40 seconds), platelet count (flow cytometry (1000/μL), normal value 150,000–450,000/μL), quick (coagulometric turbidimetry (%), normal value 70–120%) and D-dimer (latex-enhanced immunoturbidimetric assay (μg/mL), normal value <0.23 μg/mL) levels. The analyses were performed according to internal laboratory standards.

Diagnosis of PE and central venous thrombosis (CVT) was established via contrast enhanced computed tomography (CT) scans, DVT was diagnosed by means of doppler sonography. All examinations were performed and assessed by a board certified radiologist.

According to our routine protocol, D-dimer levels were regularly determined directly postoperatively and on the first postoperative day after craniotomy. In patients with a high risk of thromboembolic complications, D-dimer levels were assessed regardless of the surgery performed. Further laboratory or radiologic examinations were performed in case of significantly elevated D-dimer levels or clinical symptoms consistent with a thromboembolic complication.

Postoperative CT or magnetic resonance imaging (MRI) of the surgical area for evaluation of complications such as local hemorrhage was routinely performed in all patients undergoing craniotomy or spinal tumor resection on the first postoperative day. Further scans during the inpatient course were performed as indicated by the responsible neurosurgeon. Complications of thromboembolic events were defined as minor (moderate hypoxemia, dyspnea, local pain), major (need for admission to ICU, pulmonary/cardiac decompensation, need for extracorporeal membrane oxygenation) or fatal. Complications of anticoagulation were defined as minor (local hemorrhage without need for intervention except for adaption of anticoagulation), severe (significant hemorrhage with need for surgical intervention) or fatal.

Standard postoperative prophylaxis of thrombosis at our institution consisted of 15,000 IU unfractionated heparin/24 hours (either two doses of 7500 IU heparin subcutaneously or continuous intravenous infusion of 15,000 IU heparin) starting on the first postoperative day. Doses were increased in case of thromboembolic events to achieve semitherapeutic or full anticoagulation over the further course after consultation with the responsible neurosurgeon.

Statistical analyses were performed using SPSS Statistics 25 (IBM, NY, USA). Continuous data were presented as mean $\pm$ standard deviation (M $\pm$ SD) or median and quartiles (Q1, Q3), whereas categorical data were shown as percentages. Continuous variables were tested for equality of variances by Levene's test. Normally distributed parametric variables with equal variances were compared using the unpaired or paired *t*-test, for non-normally distributed parametric variables the Mann-Whitney-U test was performed. Variances were tested with ANOVA. Nominal variables were tested by means of Fisher's exact test. Non-parametric correlations were evaluated with Spearman's test. Variables with association at a significance level of $p < 0.05$ in the univariate analysis were entered into a stepwise logistic regression model with conditional forward selection. Receiver Operating Characteristic (ROC) analyses were performed for D-dimer levels.

3. Results

3.1 General patient characteristics

In total, 25,256 operative cases were treated at our institution between 2008 and 2017. Of these, 173 cases of adults with a diagnosed thromboembolic event (0.7%) were identified and included in the further analysis. Mean age was 64.8 $\pm$ 1.0

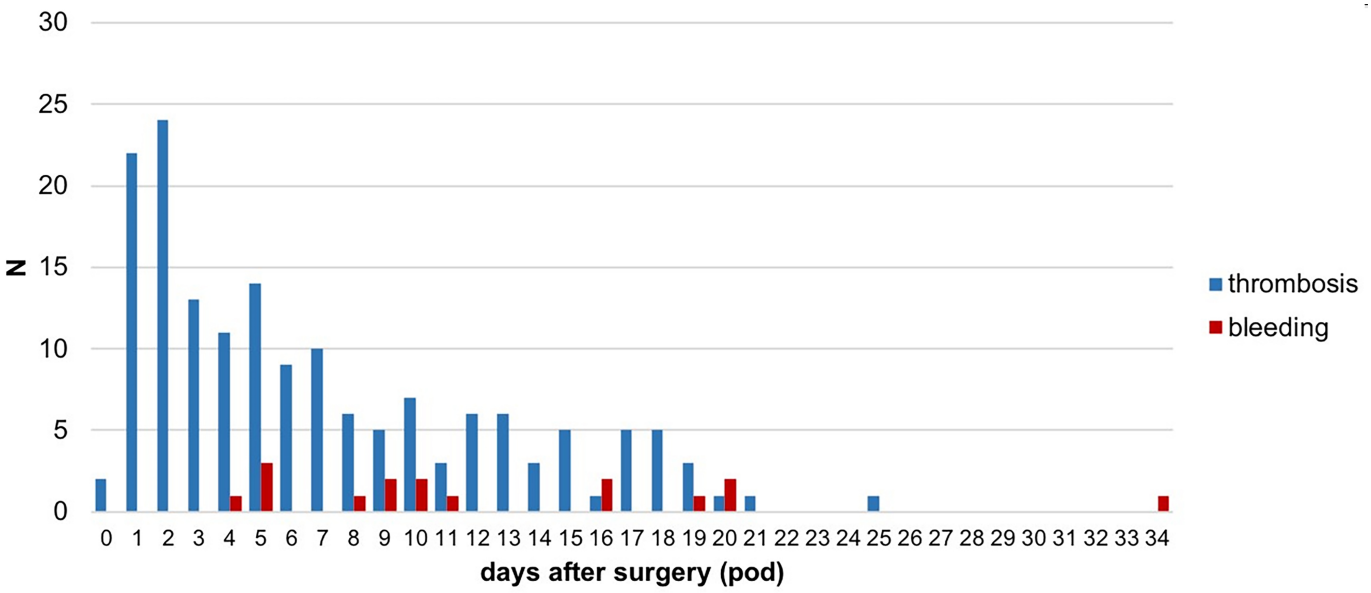

FIGURE 1. Number of thromboembolic events and bleeding events on days 0–34 after surgery.

years. Mean weight was 85.5 ± 1.4 kg. 63.6% of all patients were male, 36.4% were female. A thromboembolic event was usually diagnosed within a week of surgery (median 5.0, Q1 = 2, Q3 = 10 days, see Fig. 1). The imaging techniques used for diagnosis were, above all, CT (n = 152, 87.9%), followed by sonography (n = 17, 9.8%) and perfusion scintigraphy (n = 2, 1.2%). Complications after anticoagulation occurred at a median of 10.0 days after surgery (Q1 = 5.8, Q3 = 18.3 days) and 7.0 days after the thromboembolic event (Q1 = 2.3, Q3 = 10.5 days, see Fig. 1).

Cranial surgery was performed in 140 (80.9%) cases, spinal surgery in 32 (18.5%) and one patient received peripheral nerve surgery. The distribution of underlying pathologies requiring the initial neurosurgical intervention was as follows: 68 patients with intracranial tumors (39.3%), 4 patients with hydrocephalus (2.3%), 24 patients with spinal stenosis or disc herniation (13.8%), 4 patients with complex spinal surgeries and instrumentation (2.3%) and 4 patients with spinal tumors (2.3%). In 56 patients (32.4%), a spontaneous intracranial hemorrhage was the primary diagnosis, 12 patients (6.9%) suffered from traumatic brain injury and 1 patient (0.6%) from neuropathy. The location of the primary pathology was cranial in 140 patients (80.9%) and spinal in 33 patients (19.1%).

Assessing the intra or directly postoperative complications, we found 139 uneventful cases (80.4%). In 17 patients (9.8%), relevant hemorrhage was seen on the postoperative CT scan but no revision surgery was required. In 12 patients (6.9%), revision surgery for hemorrhage evacuation, in 2 cases (1.2%) decompressive surgery for edema was performed. Hydrocephalus was seen in 3 cases (1.7%) and external ventricular drainage was necessary.

Risk factors for thrombosis were present in 14 patients (8.1%): an underlying coagulopathy was found in 10 patients (4.8%) with 2 cases of factor V mutation, 2 cases of protein C/S deficit, 4 cases of factor XIII deficit, 1 case of hepatic synthesis dysregulation and 1 case of factor VII mutation. Medical history revealed previous thrombosis in 21 patients (12.1%). All detailed patient characteristics can be found in Table 1.

Mean D-dimer levels were found to be at 6.53 ± 1.0 mg/dL directly postoperatively with an increase to 8.1 ± 0.9 on the first postoperative day. On the day of diagnosis of the thromboembolic event, D-dimer levels were significantly higher in patients after cranial surgery as compared to spinal interventions (p = 0.04, 14 ± 17 *vs.* 8 ± 6 μg/mL). We found no significant difference of D-dimer levels in patients with or without coagulopathy or between malignant and benign tumors. Three-month-follow-up did not reveal any additional diagnoses of thrombosis.

3.2 Location and diagnosis of thrombosis

Distribution of thromboses was as follows: 12 cases of isolated deep venous thrombosis (DVT, 6.9%), 10 central vessel thromboses (CVT, 5.8%) and 151 pulmonary embolisms (PE, 87.3%) with or without the aforementioned.

In 58 cases (33.5%), elevated levels of D-dimer prompted for further diagnostics, identifying thrombosis without clinical symptoms (16.0 ± 1.5 μg/mL). In 87 cases (50.3%) clinical signs such as tachycardia, respiratory distress, reduced O_2-saturation or local signs of lower extremity thrombosis led to the diagnosis. In 28 patients (16.2%), diagnosis of thrombosis was coincidental during imaging examinations (*e.g.* CT for aspiration/pneumonia/trauma). There was no difference in initial signs and symptoms regarding the location of the thrombosis (Fisher's exact, p = 0.19, see Table 2). Also, no significant difference in laboratory parameters was found between DVT, CVT and PE on days 0–7 after diagnosis (see Fig. 2).

3.3 Complications due to thromboembolic events

Most of the patients with a thromboembolic event had no or minor symptoms (n = 108, 62.4%). In 55 cases (31.8%), clinical effect was major. Ten patients (5.8%) died due to cardiocirculatory arrest caused by significant blood flow ob-

TABLE 1. Basic patient characteristics.

Basic patient characteristics	
Weight (M ± SD)	85.5 ± 1.4 kg
body-mass index (M ± SD)	28.6 ± 6.1 kg/m^2
Age (M ± SD)	64.8 ± 1.0 years
Gender	
	36.4% female (n = 63)
	63.6% male (n = 110)
D-dimer pod 0 (M ± SD)	6.53 ± 1.0 µg/mL
D-dimer pod 1 (M ± SD)	8.1 ± 0.9 µg/mL
Diagnosis of thrombosis on pod (M ± SD)	6.8 ± 5.6 days
Diagnostic modality	
	50.3% clinical (n = 87)
	33.5% laboratory (n = 58)
	16.2% incidental on imaging (n = 28)
Imaging technique	
	87.9% CT (n = 152)
	9.8% sonography (n = 17)
	1.2% perfusion scintigraphy (n = 2)
Location of thrombosis	
	6.9% deep venous thrombosis (DVT, n = 12)
	5.8% central vessel thrombosis (CVT, n = 10)
	87.3% pulmonary embolism (PE, n = 151)
Location of DVT (n = 12)	
	83.3% femoral vein (n = 10)
	16.7% popliteal vein (n = 2)
Location of central vessel thrombosis (n =10)	
	40% inferior vena cava (n = 4))
	30% subclavian vein (n = 3)
	20% superior vena cava (n = 2)
	10% portal vein (n = 1)
Underlying neurosurgical pathology	
	39.3% intracranial tumor (n = 68)
	32.4% intracerebral hemorrhage (n = 56)
	13.8% spinal stenosis/disc prolaps (n = 24)
	6.9% traumatic brain injury (n = 12)
	2.3% hydrocephalus (n = 4)
	2.3% spinal tumor (n = 4)
	2.3% spinal instability (n = 4)
	0.6% neuropathy (n = 1)
Brain tumor histopathology (n = 68)	
	26.4% metastasis (n = 18)
	25.0% glioblastoma (n = 17)
	9.7% other glioma (n = 7)
	6.9% pituitary adenoma (n = 5)
	4.2% vestibular schwannoma (n = 3)
	2.8% lymphoma (n = 2)
	1.4% trigeminal schwannoma (n = 1)
	1.4% chordoma (n = 1)
	6.9% others (n = 5)
Risk factors of thrombosis	
	12.1% previous thrombosis (n = 21)
	4.8% coagulopathy (n = 10)
Clinical signs of thromboembolic event	
	61.8% none/minor (n = 107)
	32.4% major (n = 56)
	5.8% fatal (n = 10)

TABLE 1. Continued.

Basic patient characteristics	
Complication of anticoagulation	
	89.6% none (n = 155)
	3.0% minor bleeding (n = 5)
	6.6% severe bleeding (n = 11)
	0.6% fatal bleeding (n = 1)
	0.6% HIT II (n = 1)

HIT: heparin-induced-thrombopenia.

TABLE 2. Distribution of location of thrombosis.

Diagnosis/location of thrombosis N (%)	Incidental	Laboratory	Clinical	total
DVT	2 (16.7%)	6 (50.0%)	4 (33.3%)	12 (6.9%)
CVT	4 (40.0%)	2 (20.0%)	4 (40.0%)	10 (5.8%)
PE	22 (14.6%)	50 (33.1%)	79 (52.3%)	151 (87.3%)
total	28 (16.2%)	58 (33.5%)	87 (50.3%)	173 (100.0%)
Cranial surgery	22 (15.7%)	66 (47.1%)	52 (37.1%)	140 (80.9%)
Spinal surgery	6 (18.2%)	21 (63.6%)	6 (18.2%)	33 (19.1%)
total	28 (16.2%)	58 (33.5%)	87 (50.3%)	173 (100.0%)

CVT = central venous thrombosis or PE = pulmonary embolism as well as site of surgery (cranial or spinal) and modality/clinical signs and symptoms leading to diagnosis (incidental, laboratory or clinical).

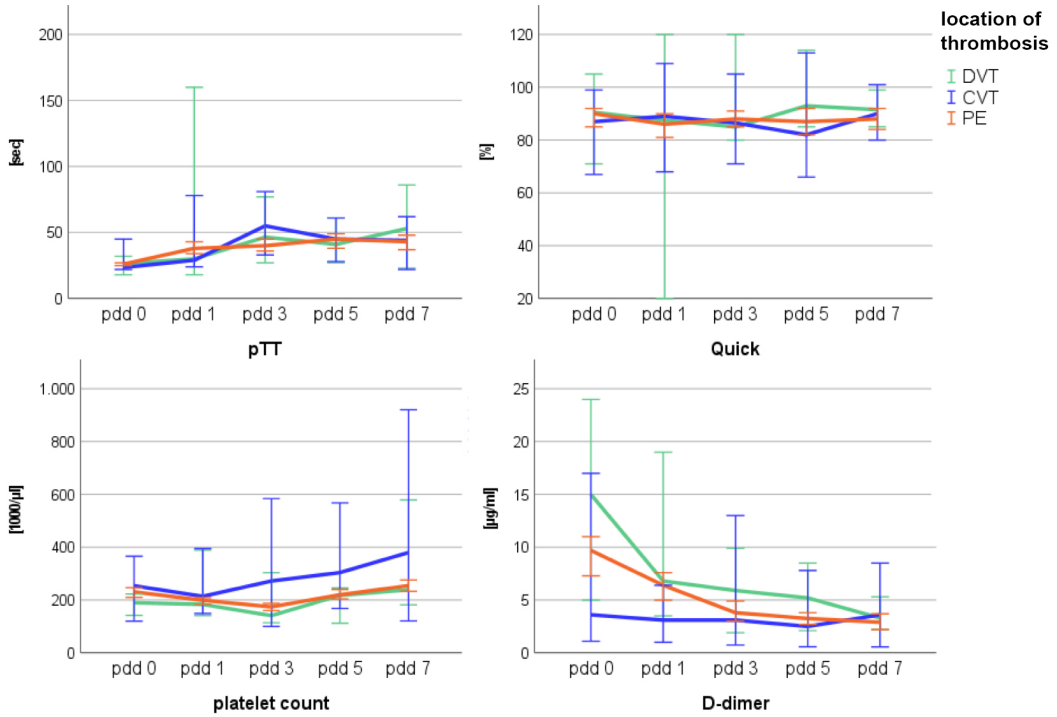

FIGURE 2. Laboratory parameters with regard to the location of the thrombosis (DVT = deep venous thrombosis, CVT = central vessel thrombosis, PE = pulmonary embolism) on days 0–7 after diagnosis. No significant difference was found between locations for pTT, Quick, platelet count or D-dimer.

struction or pulmonary decompensation.

When comparing clinical signs and symptoms with the location of the thrombosis, significantly more patients with a PE suffered from a major (35.8%, n = 54) or fatal (6.6%, n = 10) complications than patients with DVT (major: 8.3%, n = 1, fatal: 0%, n = 0) or CVT (major: 0%, n = 0, fatal: 0%, n = 0; Fisher's exact, $p = 0.02$).

Univariate analysis showed no difference in age, weight (including body-mass-index), prevalence of hypertension or gender between groups of patients with different severity of

TABLE 3. Risk factors for a fatal clinical course due to thrombosis.

Risk factors for different clinical courses of thrombosis	None or minor	Major	Fatal	Statistics
Age (M ± SD)	63.95 ± 13.87	66.11 ± 11.51	67.25 ± 10.94	F(2) = 0.82, p = 0.44
Weight (M ± SD)	84.15 ± 17.44	87.34 ± 18.47	89.56 ± 17.03	F(2) = 0.69, p = 0.50
Gender				Fisher's exact, p = 0.43
Female	41 (65.1%)	17 (27.0%)	5 (7.9%)	
Male	67 (60.9%)	38 (34.5%)	5 (4.5%)	
Coagulopathy N (%)				Fisher's exact, p = 0.049
None	102 (62.6%)	53 (32.5%)	8 (4.9%)	
Hypocoagulation	5 (83.3%)	0 (0.0%)	1 (16.7%)	
Hypercoagulation	1 (25.0%)	2 (50.0%)	1 (25.0%)	
Previous Thrombosis N (%)				Fisher's exact, p = 0.68
Yes	13 (61.9%)	6 (28.6%)	2 (9.5%)	
No	95 (62.9%)	48 (31.8%)	8 (5.3%)	
Pathology N (%)				Fisher's exact, p = 0.035
Spinal	15 (45.5%)	14 (42.4%)	4 (12.1%)	
Cranial	93 (66.4%)	41 (29.3%)	6 (4.3%)	

clinical signs of thrombosis or between fatal and non-fatal cases. Patients undergoing spinal surgery had a higher rate of major and fatal thromboses compared to patients after craniotomy (Fisher's exact, p = 0.035). Individuals with coagulopathy in their medical history presented with a higher rate of a fatal clinical course than those with unimpaired coagulation (Fisher's exact, p = 0.049). No difference in severity of clinical course was found in patients with or without thrombosis in their medical history (Fisher's exact, p = 0.68, see Table 3).

3.4 Complications of anticoagulation

After increase of heparin dosage due to thrombosis, 155 cases (89.6%) revealed an uneventful further in-patient course. In 2 cases (1.2%), minor intracranial hemorrhage was seen without need for intervention. In 3 cases (1.8%), anticoagulation therapy was temporarily discontinued. In 11 cases (6.6%), severe hemorrhage with the need for surgical intervention was diagnosed. In 1 case, hemorrhage after anticoagulation was fatal (0.6%). Another patient was diagnosed with heparin induced thrombocytopenia type II and received argatroban instead of heparin. The further course was uneventful. One fatal case of severe bleeding after anticoagulation had presented with minor signs of thrombosis. There was no association of severity of thrombosis and extent of bleeding (Fisher's exact, p = 0.44).

Severity of bleeding was not associated with location of thrombosis (Fisher's exact, p = 0.50), coagulopathy leading to bleeding tendency (Fisher's exact, p = 0.36), location of surgery (Fisher's exact, p = 0.75), gender (Fisher's exact, p = 0.43), age (Fisher's exact, p = 0.88) or weight (Fisher's exact, p = 0.45).

3.5 Laboratory markers as a monitoring tool

3.5.1 Risk of severe VTE

No significant differences of coagulation parameters were observed between the groups of patients with no or mild, major and fatal clinical signs of thrombosis on the day of surgery or the first postoperative day. However, fatal courses of thromboembolic events were associated with significantly higher levels of pTT and lower levels of quick and platelets on the day of diagnosis and day 1 after diagnosis. During the further course, no significant differences were observed (see Fig. 3 and Table 4).

3.5.2 Risk of severe bleeding

Laboratory parameters were compared between the groups of patients with no or minor bleeding and major or fatal bleeding. No difference was found on the day of surgery or the first postoperative day. On the day of diagnosis of the thromboembolic event, pTT was significantly lower in the group with major bleeding. D-dimer differed significantly between the two groups on all days after diagnosis with higher levels in the group with severe or fatal bleeding (see Fig. 4 and Table 5).

Laboratory markers were also assessed on days 0–7 after complication due to anticoagulation and did not show any significant difference between the groups with minor and major or fatal bleeding.

D-dimer levels were highest in both groups of patients with no or minor and severe or fatal bleeding on pdd0 and decreased during the following days. Levels remained relatively stable after pdd3 with higher levels in the group with major or fatal bleeding.

A cut-off was found for D-dimer levels at 4.95 μg/mL on pdd3 (AUC = 0.726, sensitivity = 0.800, specificity = 0.678, p = 0.003) with higher risk of a severe bleeding complication in patients with D-dimer higher than this value. After removing patients with a postoperative bleeding as a possible confounding factor, the same cut-off could be defined with even higher

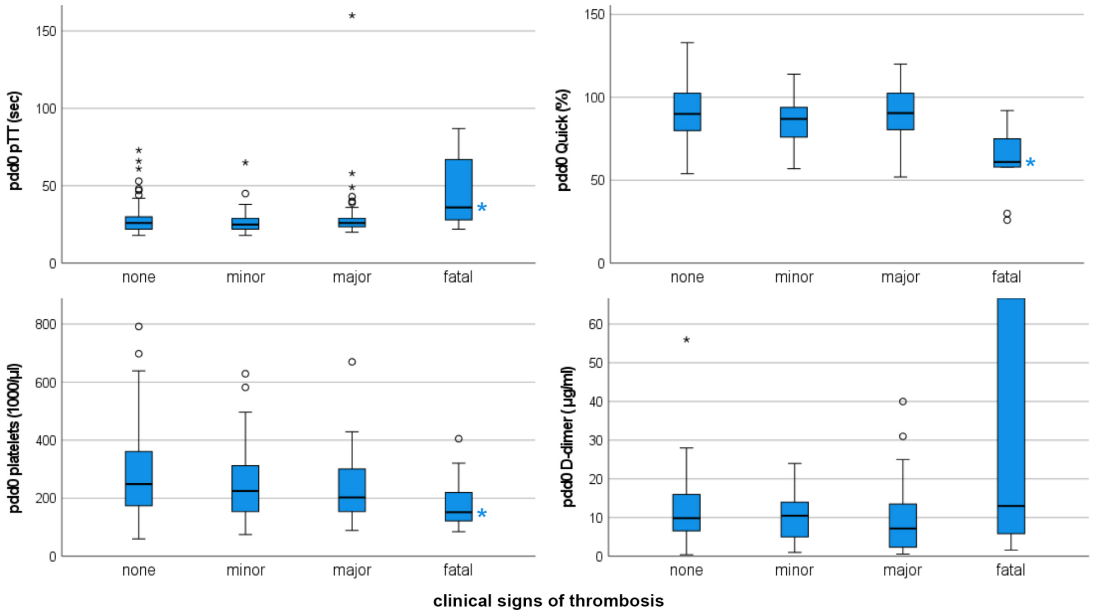

FIGURE 3. Laboratory parameters of patients with no symptoms, minor, major and fatal further clinical course due to VTE on the day of diagnosis (pdd0).

TABLE 4. M ± SD of laboratory markers on day 0 (pdd0) and 1 (pdd1) after diagnosis of thrombosis in the groups of patients with no symptoms or minor, major and fatal course due to VTE.

Laboratory markers and clinical course of thrombosis	None or minor (M ± SD)	Major (M ± SD)	Fatal (M ± SD)	Statistics
pTT (pdd0)	28.29 ± 10.30	30.52 ± 20.45	46.67 ± 23.84	H(2) = 8.03, p = 0.02
pTT (pdd1)	45.64 ± 32.15	50.60 ± 29.28	58.86 ± 25.95	H(2) = 7.73, p = 0.02
Platelets (pdd0)	284.00 ± 152.57	230.60 ± 106.18	193.44 ± 107.41	H(2) = 6.59, p = 0.04
Platelets (pdd1)	295.58 ± 159.62	227.05 ± 80.07	178.50 ± 100.89	H(2) = 7.94, p = 0.02
Quick (pdd0)	88.83 ± 15.78	91.13 ± 15.71	62.00 ± 22.42	H(2) = 13.39, p = 0.001
Quick (pdd1)	86.60 ± 17.70	87.92 ± 15.46	67.71 ± 18.70	H(2) = 6.70, p = 0.04
D-dimer (pdd0)	12.79 ± 13.18	10.87 ± 13.56	34.91 ± 37.55	H(2) = 4.16, p = 0.13
D-dimer (pdd1)	8.63 ± 7.80	10.40 ± 19.29	5.13 ± 1.95	H(2) = 2.12, p = 0.35

TABLE 5. M ± SD of laboratory markers on day 0 to 7 (pdd0–7) after diagnosis of thrombosis in the groups of patients with no or minor and severe or fatal bleeding complications after anticoagulation.

Extent of bleeding complication	None or minor (M ± SD)	Severe or fatal (M ± SD)	Statistics
pTT (pdd0)	30.39 ± 15.76	23.50 ± 2.99	U = 458.00, Z = −2.10, p = 0.04
pTT (pdd1)	48.86 ± 31.81	36.17 ± 14.02	U = 681.50, Z = −1.21, p = 0.23
Platelets (pdd0)	263.06 ± 141.38	245.60 ± 119.27	U = 693.50, Z = −0.16, p = 0.87
Platelets (pdd1)	267.32 ± 141.31	270.00 ± 134.12	U = 557.00, Z = 0.12, p = 0.91
Quick (pdd0)	88.38 ± 17.44	82.50 ± 14.59	U = 587.00, Z = −1.18, p = 0.24
Quick (pdd1)	86.39 ± 17.55	83.75 ± 15.96	U = 753.00, Z = −0.60, p = 0.55
D-dimer (pdd0)	13.04 ± 16.68	17.18 ± 8.13	U = 1175.50, Z = 2.59, p = 0.01
D-dimer (pdd1)	8.90 ± 13.25	11.35 ± 6.44	U = 803.50, Z = 2.13, p = 0.03
D-dimer (pdd3)	4.62 ± 4.02	7.25 ± 4.15	U = 631.50, Z = 2.33, p = 0.02
D-dimer (pdd5)	3.90 ± 3.36	5.85 ± 4.76	U = 625.50, Z = 1.97, p = 0.049
D-dimer (pdd7)	3.74 ± 3.34	5.83 ± 3.38	U = 504.50, Z = 2.05, p = 0.04

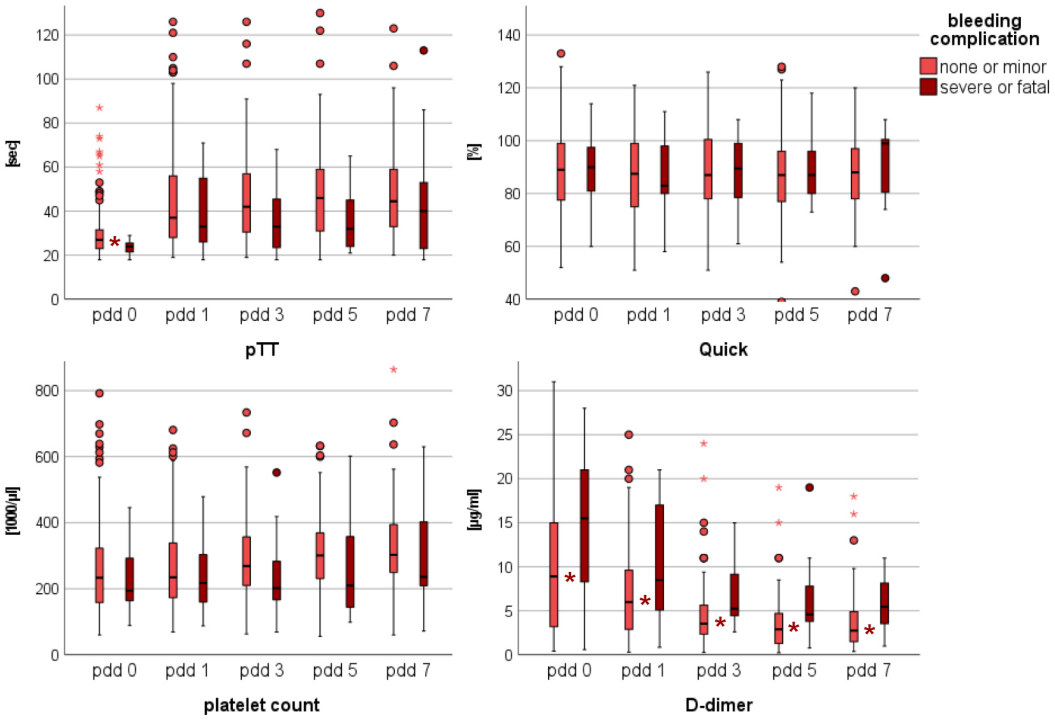

FIGURE 4. Laboratory parameters of patients with no or minor and severe or fatal bleeding complications after anticoagulation on days 0–7 after diagnosis of thrombosis.

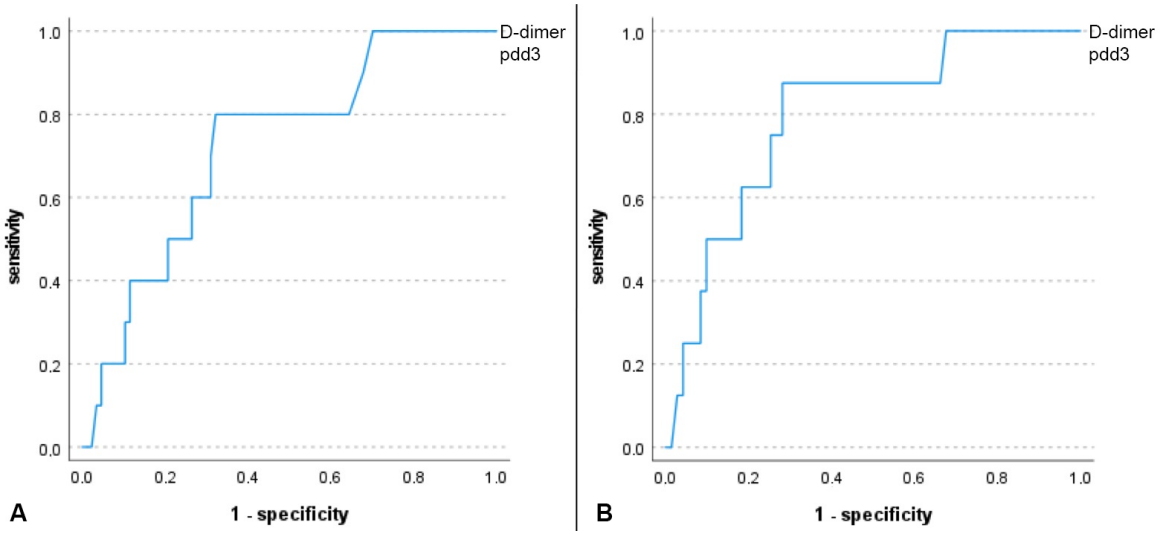

FIGURE 5. ROC curve of D-dimer on day 3 after diagnosis of thrombosis (pdd3). Cut-off for no/minor and severe/fatal bleeding complications = 4.95 µg/mL. A: before (AUC = 0.726, sensitivity = 0.800, specificity = 0.678, $p = 0.003$), B: after correction of postoperative bleeding (AUC = 0.796, sensitivity = 0.875, specificity = 0.704, $p < 0.001$).

sensitivity and specificity (AUC = 0.796, sensitivity = 0.875, specificity = 0.704, $p < 0.001$, see Fig. 5).

A moderate negative correlation of D-dimer and pTT was found on pdd 0–7 (pdd0: Spearman's $\rho = -275$, $p < 0.001$, pdd1: Spearman's $\rho = -0.371$, $p < 0.001$, pdd3: Spearman's $\rho = -485$, $p < 0.001$, pdd5: Spearman's $\rho = -0.417$, $p < 0.001$, pdd7: Spearman's $\rho = -0.228$, $p = 0.04$).

3.5.3 Prognostic factors for major complications due to thrombosis

Univariate analysis determined location of the thrombosis, site of surgery, coagulopathy in medical history and the laboratory parameters pTT, quick and platelets on pdd 0 and 1 to be associated with a worse clinical course after VTE. Stepwise binary logistic regression showed spinal surgery, pulmonary embolism and platelet count on pdd0 to be associated with a major or fatal course of thrombosis ($\chi^2(6) = 29{,}997$, $p < 0.001$).

4. Discussion

In this study of 173 cases with postoperative DVT or VTE after a neurosurgical procedure, we identified several risk factors associated with a severe clinical course. Furthermore, laboratory parameters associated with hemorrhagic complications of anticoagulation were found. Routine laboratory coagulation markers during the immediate postoperative course were shown not to be able to predict outcome. D-dimer levels after diagnosis of thrombosis decreased gradually in all patients, consistent with the start of anticoagulation therapy. A decrease of D-dimer due to heparin has been shown before [11]. However, this study showed higher D-dimer-concentrations after initiation of heparin therapy in patients suffering from a major bleeding complication. A cut-off of 4.95 μg/mL on day 3 after diagnosis of the VTE was defined. Earlier studies were able to show, that D-dimer correlate with the thrombolytic activity in the body [14], which might explain our observation. Interestingly, D-dimer at the time of diagnosis of VTE or the following days did not predict the severity of outcome. However, higher pTT, lower quick and lower platelet count thus a deterioration of the coagulation ability as a sign of a progressed stage of consumption coagulopathy were associated with a major or fatal course. Consumption coagulopathy and disseminated intravascular coagulation are known to be associated with unfavorable outcome and can be present in fatal pulmonary embolism [15, 16] as shown in our cohort.

In general, therapeutic pTT-guided unfractionated heparin therapy is the standard of care treatment during the early phase after diagnosing a DVT or VTE and preferred in postoperative patients due to the shorter half-life compared to low molecular weight heparin [17]. Since neurosurgical patients are at a very high bleeding risk, especially during the early postoperative phase, determining the dosage of heparin therapy can be challenging [3, 15, 17]. In this study, pTT was not associated with incidence of bleeding complications. Mean pTT levels were even lower in the group of patients with severe or fatal bleeding and did not attain therapeutic levels of 60–80 seconds. A cut-off for pTT was not found. Therefore, pTT might be a good indicator to monitor anticoagulation but not to determine the risk of bleeding complications in postoperative neurosurgical patients.

In this cohort, DVT or VTE was detected more frequently in patients after craniotomy (80.9%) as compared to patients after spinal surgery. Spinal location of the neurosurgical procedure was an independent risk factor for a worse clinical course of thrombosis. A possible explanation might be a selection bias, as patients undergoing spinal surgery receive routine D-dimer examinations less frequently than patients after craniotomy according to our institution's standard protocol. Therefore, fewer subclinical courses might have been detected and only severe cases were diagnosed and thus included in our analysis. On the other hand, Table 2 shows, that clinical presentation of DVT or VTE was more common after cranial surgery and laboratory diagnosis of thrombosis was more frequent in spinal patients. The timing of laboratory examination after surgery was not assessed in this retrospective study. Therefore, routine D-dimer screening on the first postoperative day might be beneficial in patients who underwent spinal surgery and possibly detects DVT or VTE earlier.

The high rate of pulmonary embolism ($\pm$ DVT) as compared to solitary DVT or CVT in this study is most likely explained by the diagnostic algorithm and might be lower in screening groups [1]. Also, the total rate of DVT or VTE (0.7%) in this study was, as expected, much lower than in screening cohorts [1, 2].

The limitations of our study arise mainly from its retrospective character. No systematic screening for VTE was performed, leading to a high rate of undetected, thus underreported cases. Assessing the patients' medical history, 3-month follow-up in this cohort did not reveal any additional diagnoses but secondary thrombosis is not routinely radiologically investigated and may be underreported. No active follow-up was performed concerning this issue. Also, there was no control group of patients without a VTE, since the purpose of this work was to investigate the course of patients with different severity of VTE and the resulting complications. Also, confounders such as infections and low Karnofsky performance score may be underreported and thus underrepresented in our data. Therefore, we see this as an important and critical issue. Implementation of further screening tools into routine postoperative care will certainly lead to many additional diagnoses of VTE. Consequently, these patients need to receive therapeutic anticoagulation which might in turn lead to a higher rate of bleeding complications.

5. Conclusions

In this study, risk factors for a major or fatal course in early postoperative DVT and VTE after neurosurgical procedures were investigated. Patients with a major or fatal VTE showed laboratory signs of consumption coagulopathy at the time of diagnosis. D-dimer did not predict the severity of VTE but a delayed decrease of D-dimer was associated with a higher risk of bleeding complications due to anticoagulation. PTT was not associated with the extent of bleeding complications. D-dimer levels higher than 4.95 μg/mL on day 3 after diagnosis and initiation of therapeutic anticoagulation were associated with severe or fatal bleeding complications. Our findings confirm that therapeutic anticoagulation in neurosurgical patients during the early postoperative phase remains challenging and cannot be solely pTT-based since treatment protocols are still lacking. PTT might be a good parameter for monitoring unfractionated heparin therapy but not to determine the risk of bleeding complications during the early postoperative phase in neurosurgical patients suffering from a DVT or VTE. D-dimer might be of use to detect early bleeding complications. Further prospective data is needed to assess this issue.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

UB, JS, FHE—designed the research study; DG, JZ—performed the research; DG, HH—analyzed the data; JZ, DG, HH—wrote the manuscript; MT, FHE, UB, JS—reviewed and supervised the manuscript, all authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the ethics committee of the medical faculty of the university of Tuebingen August 15th 2018 (624/2018BO2). Informed patient consent was not required for this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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