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Frequency and treatment of venous thromboembolic events in patients with space-occupying brain infarction and decompressive craniectomy

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ABSTRACT

Introduction Venous thromboembolic events (VTEs) like deep vein thrombosis or pulmonary embolism are frequent complications in (neuro) critical ill patients. Anticoagulation for VTE after space-occupying brain infarction is a therapeutic dilemma. The aim of this retrospective study was to investigate the frequency of clinically apparent VTE in patients with acute ischaemic stroke (AIS) due to large vessel occlusion (LVO), its treatment, and the rate of complications.

Methods Patients with first AIS due to LVO were assigned to one of the following groups: space-occupying brain infarction with (1) or without (2) decompressive craniectomy (DC), AIS comprising more than 2/3 (3) or less than 2/3 (4) of the middle cerebral artery territory. Clinically obtained parameters included risk factors for VTE, type of thromboprophylaxis, treatment of VTE and treatment-associated complications.

Results 15 of 173 (8.7%) patients had a VTE, which was diagnosed 10.9 ± 7.2 days after admission. Patients with a space-occupying brain infarction and DC had significantly more VTE (n=11/63; 17.5%) than patients with a space-occupying brain infarction without DC (0/26; p =0.023) or patients without DC (4/110; 3.6%; p = 0.004). Younger age, DC and cumulative duration of central venous catheter were identified as risk factors for VTE. Only three patients had major bleeding events while being anticoagulated (one asymptomatic cerebral and two extracranial bleedings).

Discussion Patients with space-occupying brain infarction and DC hold a high risk for VTE. Despite extensive infarct size and DC, therapeutic anticoagulation required for VTE appeared to be safe regarding intracranial bleeding complications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with space-occupying brain infarction after ischaemic stroke often require decompressive craniectomy (DC) to alleviate intracranial pressure.
⇒ Immobility and neurosurgical intervention increase the risk of venous thromboembolic events (VTEs), which can occur in up to 35% of cases, often undetected, with fatal pulmonary embolism frequently identified postmortem.
⇒ Balancing the risks of intracranial bleeding and VTE, particularly when starting anticoagulation, remains challenging, with limited data on post-DC bleeding risks.

WHAT THIS STUDY ADDS

⇒ Patients who undergo DC have a significantly higher risk of VTE, but therapeutic anticoagulation appears feasible without major intracranial bleeding complications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may encourage earlier thromboprophylaxis and, in case of VTE, also earlier anticoagulation in patients with space-occupying brain infarction and DC, while prompting further research to refine anticoagulation strategies in this high-risk population.

INTRODUCTION

Venous thromboembolic events (VTEs), which comprise deep vein thrombosis (DVT) and pulmonary embolism (PE), are dreaded complications in the treatment of critically ill patients.[1] Despite pharmacological prophylaxis, the frequency of VTE in intensive care units (ICUs) may considerably vary, ranging from 4.2% in predominantly conservatively treated patients, to 9.1% in patients with traumatic brain injury,[2] to even 35% in patients with space-occupying brain infarction undergoing decompressive craniectomy (DC).[3 4] Without screening, DVT may remain clinically unsuspected in many patients and fatal PE was often diagnosed postmortem.[5] On the other hand, regular screening would probably identify more patients with DVT who would not have developed complications like PE.

Although the implementation of endovascular treatment (EVT) in the routine treatment of patients with ischaemic stroke due to large vessel occlusion (LVO) resulted in a decreased mortality and morbidity,[6] there are still patients developing a space-occupying brain infarction who will require DC.[7] These patients hold at least two major risk factors for

VTE: immobility due to the severe ischaemic stroke and neurosurgical intervention.[2 8] In case of a VTE in neurocritical ill patients with extensive, space-occupying brain infarction and DC, physicians are between Scylla and Charybdis considering the start of therapeutic anticoagulation, thus weighing the risk of intracranial bleeding against the risk of PE. Moreover, the frequency of bleeding complications in patients with space-occupying cerebral infarction undergoing DC and anticoagulation is unknown, which impedes a proper risk–benefit estimation.

Aim of this retrospective study was to investigate the frequency of VTE in patients with cerebral infarction due to proximal LVO with and without DC, to identify risk factors for VTE and to assess the rate of anticoagulation-associated complications.

METHODS

Data acquisition

This retrospective, non-interventional, explorative study was performed according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendment.

Hospital-based medical records of patients with acute ischaemic stroke treated in the neuro-ICU of a tertiary hospital between January 2012 and December 2021 were screened. Inclusion criteria were (1) age >18 years, (2) first ischaemic stroke due to LVO (internal carotid artery or middle cerebral artery (MCA)), (3) onset of stroke symptoms less than 24 hours before admission and (4) no intracranial bleeding (either haemorrhagic infarction or parenchymal haemorrhage) on the first follow-up CT. Patients were then stratified into four groups according to the size of their ischaemic stroke and their treatment:

- Group 1: Patients with space-occupying brain infarction with DC.
- Group 2: Patients with space-occupying (midline shift ≥5 mm) brain infarction without DC.
- Group 3: Patients with infarction of more than 2/3 of the territory of the MCA but without a relevant (<5 mm) midline shift.
- Group 4: Patients with infarction of less than 2/3 of the territory of the MCA.

In addition to demographic data, medical history, clinical data obtained during the hospital stay, information regarding stroke treatment (intravenous thrombolysis, mechanical thrombectomy and associated parameters) were extracted from medical records.

Diagnosis of VTE had to be confirmed by either CT or duplexsonography. VTE was considered symptomatic in case typical clinical signs existed like for DVT local pain, reddening, swelling, an increased circumference of the extremity, skin warming or in case of PE chest pain, dyspnoea, hypotension, acute heart failure or cardiac arrest. Typically, these symptoms led to the clinical suspicion of VTE that had to be confirmed by subsequent imaging. On the other hand, the diagnosis of a VTE was considered incidental when clinical signs were missing and the indication for imaging was due to another reason than the search for a thrombosis, for example, the indication for a chest CT scan was to find the focus of an infection and not to detect PE, or when a central venous catheter-associated thrombosis in the internal jugular vein was found during the ultrasound examination of the carotid arteries. In case patients had more than one VTE, for example, a PE and a DVT, this was counted only as one event (in this case as a PE).

Statistics

SPSS (V.29.0, IBM) was used for statistical calculations. After descriptive analyses, statistical significance between groups was assessed by χ^2 test for categorical variables and by t-test or Mann-Whitney U-test, depending on whether the respective parameters were normally distributed or not. A $p<0.05$ was considered statistically significant.

RESULTS

We identified 183 patients with LVO that fulfilled the inclusion criteria of whom 10 had to be excluded due to missing imaging data, thus finally resulting in 173 patients with LVO. Patients with space-occupying brain infarction and DC were significantly younger (age±SD: group 1: 60.1 ± 10.6 vs group 2: 73.6 ± 10.7, group 3: 74.3 ± 11.8, group 4: 73.4 ± 9.6 years; Kruskal-Wallis test, p <0.001; table 1). At admission, patients with space-occupying brain infarction without DC showed the highest National Institute of Health Stroke Scale (NIHSS) score (22.3 ± 9.4; Kruskal-Wallis test, p = 0.021) and the highest Simplified Acute Physiology Score (SAPS 2: 37.5 ± 13.4; Kruskal-Wallis test, p = 0.027; table 1). Considering the treatment, 42.2% of all patients received systemic thrombolysis with no differences between groups, and 64.7% underwent EVT. EVT was significantly more frequent in patients with infarction of less than 2/3 of the MCA territory than in patients who underwent DC (88.1% vs. 46.0%, χ^2 test, p <0.001; table 1). Altogether 15 of 173 (8.7%) patients had a VTE. VTE was diagnosed 10.9 ± 7.2 days after admission. All patients with VTE were on pharmacological thromboprophylaxis (unfractionated heparin (UFH) in three patients, low-molecular-weight heparin (LMWH) in seven patients and fondaparinux in five patients). No patient with VTE was treated with intermittent pneumatic compression (IPC) before. Patients with a space-occupying brain infarction and DC had significantly more VTE (n = 11/63; 17.5%) than patients with a space-occupying brain infarction without DC (0/26; Fisher's exact test, p = 0.023), or patients without DC (4/110; 3.6%; Fisher's exact test, p = 0.004). In patients with space-occupying brain infarction and DC, VTE was diagnosed 9.5 ± 6.1 days after admission, respectively, 7.7 ± 6.4 days after DC. Nine of 11 (81.8%) patients with a space-occupying brain infarction undergoing DC and with VTE were clinically suspicious for a VTE. In contrast, in all four patients with VTE but without DC (two PE and two central venous catheter-associated

Table 1 Baseline characteristics of the study population

	All	Space-occupying brain infarction		Non-space-occupying brain infarction		P value
	N = 173	with DC (n = 63)	without DC (n = 26)	>2/3 of MCA territory (n = 25)	<2/3 of MCA territory (n = 59)	
Age in years (mean ± SD)	68.7 ± 12.3	60.1 ± 10.6	73.6 ± 10.7	74.3 ± 11.8	73.4 ± 9.6	<0.001
Sex (female (%))	68 (39.3)	24 (38.1)	9 (34.6)	9 (36.0)	26 (44.1)	0.0812†
Pre-mRS (mean ± SD)	0.5 ± 1.1	0.4 ± 0.8	0.9 ± 1.3	0.6 ± 1.2	0.5 ± 1.2	0.327
NIHSS at admission (mean ± SD)	18.2 ± 8.4	18.3 ± 7.4	22.3 ± 9.4	16.5 ± 8.8	16.8 ± 8.3	0.021
Systemic thrombolysis (n (%))	73 (42.2)	23 (36.5)	12 (46.2)	10 (40.0)	28 (47.5)	0.632†
EVT (n (%))	112 (64.7)	29 (46.0)	14 (53.8)	17 (68.0)	52 (88.1)	<0.001†
First APACHE II (mean ± SD)	12.7 ± 4.6	11.9 ± 4.8	13.8 ± 4.9	13.4 ± 4.3	12.8 ± 4.5	0.365
First SAPS 2 (mean ± SD)	32.7 ± 11.5	29.8 ± 10.9	37.5 ± 13.4	34.9 ± 12.2	32.7 ± 10.1	0.027
Arterial hypertension (n (%))	140 (80.9)	46 (73.0)	21 (80.8)	24 (96.0)	49 (83.1)	0.093†
Current smoking (n (%))	50 (28.9)	30 (47.6)	4 (15.4)	6 (24.0)	10 (16.9)	<0.001†
Atrial fibrillation (n (%))	43 (24.9)	9 (14.3)	8 (30.8)	8 (32.0)	18 (30.5)	0.114†
Anticoagulation at admission (n (%))	36 (20.8)	11 (17.5)	4 (15.4)	6 (24.0)	15 (25.4)	0.624†
Carcinoma						
Active (n (%))	9 (5.2)	4 (6.3)	1 (3.8)	2 (8.0)	2 (3.4)	
Status post (n (%))	20 (11.6)	5 (7.9)	6 (23.1)	2 (8.0)	7 (11.9)	
None (n (%))	144 (83.2)	54 (85.7)	19 (73.1)	21 (84.0)	50 (84.7)	
DVT in medical history (n (%))		2 (3.2)	2 (7.7)	2 (8.0)	3 (5.1)	0.741†
PE in medical history (n (%))		2 (3.2)	0	2 (8.0)	1 (1.7)	0.332†

*Kruskal-Wallis test.
†$\chi 2$ test.
APACHE, Acute Physiology And Chronic Health Evaluation; DC, decompressive craniectomy; DVT, deep vein thrombosis; EVT, endovascular treatment; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PE, pulmonary embolism; SAPS 2, Simplified Acute Physiology Score 2.

thrombosis), VTEs were found incidentally. Among the 11 patients with space-occupying brain infarction and DC, 3 (27.3%) patients had a central venous catheter-associated thrombosis, 3 (27.3%) patients solely had a DVT and 5 (45.5%) patients had PE (figure 1). We found no protective effect of a preceding systemic thrombolysis on the frequency or the timing of VTEs. There were 7 VTEs in 73 patients (9.6%) with alteplase treatment vs. 8 VTEs in 100 patients (8.0%) without alteplase treatment (χ^2 test, p = 0.741). VTEs were diagnosed 9.3 days after admission in patients with systemic thrombolysis compared with 12.3 days after admission in patients without systemic thrombolysis.

Analysing risk factors, patients with VTE were significantly younger (60.2 ± 10.5 vs. 69.5 ± 12.2 years, Mann-Whitney-U test, p = 0.004; table 2), had more often undergone DC (73.3% vs. 26.6%, χ^2 test, p <0.001; table 2), and the cumulative duration of central venous catheter was longer (21.2 ± 9.4 days vs 13.2 ± 8.4 days, Mann-Whitney U test, p = 0.003; table 2).

After the diagnosis of VTE, therapeutic anticoagulation was immediately initiated in all patients: 13 (86.7%) patients received UFH, 1 (6.7%) patient was anticoagulated with LMWH and 1 (6.7%) patient with fondaparinux (table 3). In case of therapeutic anticoagulation with UFH, the targeted range of the activated partial thromboplastin

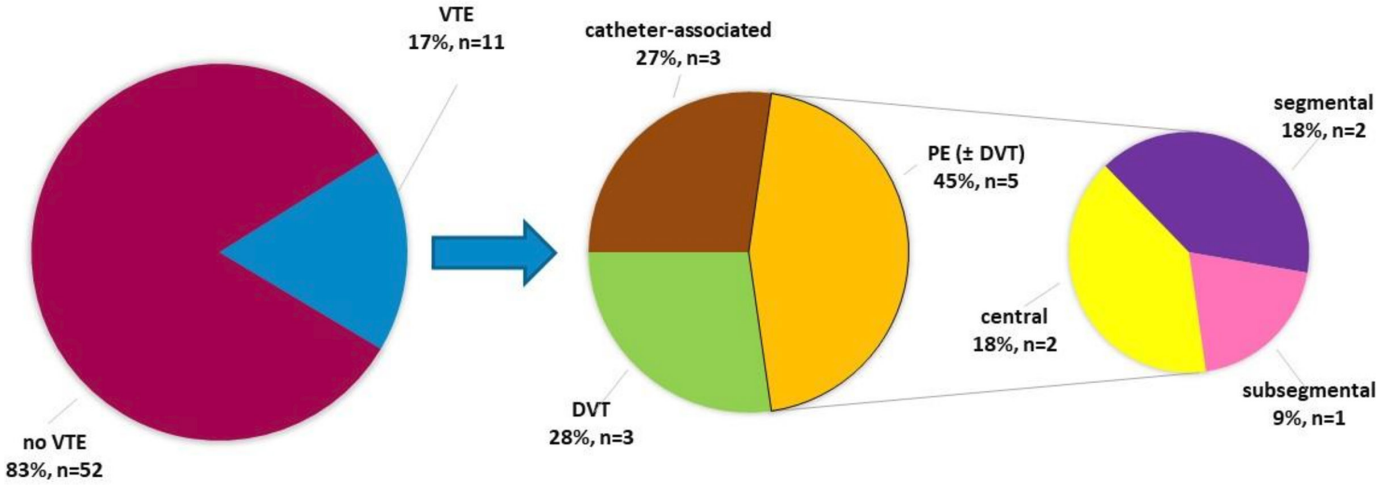

Figure 1 Characterisation of venous thromboembolic events (VTEs) in patients with space-occupying brain infarction and decompressive craniectomy. DVT deep vein thrombosis, PE pulmonary embolism.

time (aPTT) was 50–60 s in nine patients, 50 s in two patients, 40–50 s in one patient and 60–80 s in one patient (table 3). Bleeding complications occurred in 3 of 15 patients: one asymptomatic intracerebral haemorrhage into the infarcted tissue and two extracranial bleedings (one splenic haemorrhage with haematoperitoneum and one patient with a bleeding from a duodenal ulcer). All three patients with bleeding complications were

Table 2 Comparison of demographic and clinical data between patients with/without venous thromboembolic events (VTEs)

	Patients with VTE (n=15)	Patients without VTE (n=158)	Significance (p value)
Age in years (mean ± SD)	60.2 ± 10.5	69.5 ± 12.2	0.004*
Sex (female (%))	4 (26.7)	64 (40.5)	0.294†
Pre-mRS (mean ± SD)	0.3 ± 0.7	0.6 ± 1.1	0.600*
First NIHSS (mean ± SD)	16.6 ± 7.6	18.3 ± 8.4	0.187*
Systemic thrombolysis (n (%))	7 (46.7)	66 (41.8)	0.714*
EVT (n (%))	11 (73.3)	101 (63.9)	0.466†
Decompressive hemicraniectomy (n (%))	11 (73.3)	42 (26.6)	<0.001†*
First APACHE II (mean ± SD)	12.1 ± 4.0	12.7 ± 4.7	0.623*
First SAPS 2 (mean ± SD)	28.9 ± 6.0	33.0 ± 11.8	0.193*
Arterial hypertension (n (%))	11 (73.3)	129 (81.6)	0.434†
Current smoking (n (%))	5 (33.3)	45 (28.5)	0.691†
Atrial fibrillation (n (%))	2 (13.3)	41 (25.9)	0.280†
Anticoagulation at admission (n (%))	1 (6.7)	35 (22.2)	0.158†
Carcinoma			
Active (n (%))	4 (26.7)	5 (3.2)	
Status post (n (%))	2 (13.3)	18 (11.4)	
None (n (%))	9 (60.0)	135 (85.4)	
DVT in medical history (n (%))	2 (13.3)	7 (4.4)	0.138†
PE in medical history (n (%))	1 (6.7)	4 (2.5)	0.361†
Duration of central venous catheters in days (mean ± SD)	21.2 ± 9.4 n = 14 (93.3 %)	13.2 ± 8.4 n = 121 (76.6%)	0.003*
Interval from admission to first (passive) mobilisation to the edge of the patient's bed (in days, mean ± SD)	11.1 ± 11.3	3.8 ± 7.3	0.496*

*Mann-Whitney U test.
†$\chi 2$ test.
APACHE, Acute Physiology And Chronic Health Evaluation; DVT, deep vein thrombosis; EVT, endovascular treatment; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PE, pulmonary embolism; SAPS 2, Simplified Acute Physiology Score 2.

Table 3 Overview over the individual characteristics, treatment data and complications in patients with venous thromboembolic events (VTEs)

Case	Age, sex	History of VTE	DC	Location of VTE	Anticoagulation	Target aPTT (in seconds)	Complications
1	40–49, f	PE	Yes	DVT, PE	UFH	50–60	–
2	70–79, m	–	Yes	DVT, PE	UFH	50–60	Splenic haemorrhage and rupture after initial splenic infarction
3	50–59, m	–	Yes	DVT	UFH	60–80	–
4	40–49, m	DVT	Yes	PE	LMWH	–	–
5	40–49, m	–	Yes	Central venous catheter (femoral vein)	UFH	50	–
6	60–69, f	–	Yes	Central venous catheter (femoral vein)	UFH	50	–
7	60–69, f	–	Yes	Central venous catheter (femoral vein)	UFH	40–50	–
8	60–69, m	–	Yes	DVT	UFH	50–60	Asymptomatic intracranial bleeding into the infarcted tissue
9	50–59, m	–	Yes	PE	UFH	50–60	–
10	50–59, m	–	Yes	DVT	UFH	50–60	–
11	60–69, m	–	Yes	PE	UFH	50–60	–
12	60–69, m	–	No	Central venous catheter (internal jugular vein)	UFH	50–60	–
13	60–69, f	DVT	No	PE	Fondaparinux	–	–
14	70–79, m	–	No	Central venous catheter (internal jugular vein)	UFH	50–60	–
15	50–59, m	–	No	PE	UFH	50–60	Bleeding from a duodenal ulcer

aPTT, activated partial thromboplastin time; DC, decompressive craniectomy; DVT, deep vein thrombosis; f, female; LMWH, low-molecular-weight heparin; m, male; PE, pulmonary embolism; UFH, unfractionated heparin.

anticoagulated with UFH with a targeted aPTT of 50–60 s. In addition, in case the thrombosis was associated with a central venous catheter, the catheter was removed after starting the anticoagulation.

DISCUSSION

The main finding of this study was that even without a systematic screening and despite regularly applied pharmacological thromboprophylaxis, patients with space-occupying brain infarction and DC had an increased rate of VTE. Furthermore, therapeutic anticoagulation in patients with space-occupying brain infarction and DC seemed to be reasonable with no symptomatic intracranial haemorrhage (ICH) and only 1 (9.1%) severe extracranial bleeding.

VTEs are frequently detected in neurocritically ill patients, in particular, when there is a systematic screening. Despite thromboprophylaxis with UFH and additional IPC, Chalouhi *et al*[4] reported a frequency for all (symptomatic and asymptomatic) VTE of 35% in patients

with space-occupying brain infarction and DC when a systematic screening for DVT was performed at 5-day intervals. About 37% of patients with VTE had a symptomatic PE, and VTE was diagnosed 7.9 days after DC.[4] In a mixed cohort of neurocritically ill patients who received thromboprophylaxis with LMWH, the frequency of DVT was 35.7%, while the frequency of PE was 17.5%, when performing a systematic screening 7 days after admission.[8] Overall, one of three neurocritically ill patients, and in particular those with space-occupying brain infarction and DC, suffer from VTE. In another study with neurosurgical patients, the routine weekly screening for DVT identified more patients with lower-extremity DVT (10% vs 3%) but did not result in less PE (2% in both groups).[9]

Due to this high risk of VTE in neurocritically ill patients, an adequate thromboprophylaxis is of utmost importance. Generally, pharmacological thromboprophylaxis reduced the risk for VTE in critically ill patients.[10] Comparing UFH with LMWH, dalteparin significantly decreased the rate of PE but not of DVT in critically ill patients.[11] Recently, in a retrospective study of patients with acute ischaemic stroke, enoxaparin significantly reduced the rate of symptomatic VTE when compared with UFH.[12] Thus, guidelines recommend pharmacological thromboprophylaxis with LMWH over UFH to prevent VTE in critically ill patients.[13 14] However, the best way to administer pharmacological thromboprophylaxis is not clear. Although LMWH was superior to UFH,[11] its bioavailability could be limited in deeply sedated patients who need vasopressors due to a restricted blood circulation in the skin.[15] Focusing on neurosurgical patients, several studies reported no increased risk of major bleeding complications, when thromboprophylaxis was initiated within 24 hours after cerebral surgery.[16 17]

Non-pharmacological thromboprophylactic measures comprise IPC, mechanical stockings, and placement of inferior vena cava filter. The use of IPC significantly decreased the rates of proximal DVT in immobile patients with acute (ischaemic and haemorrhagic) stroke from 12.1% to 8.5%.[18] IPC was also superior to no specific treatment in the prevention of VTE in patients undergoing neurosurgical procedures.[19] Thus, in patients undergoing craniectomy who are at a high thrombotic risk, guidelines recommend a combination of mechanical and pharmacological thromboprophylaxis with IPC to be started perioperatively and LMWH to be added within the first 24 hours after surgery.[20] Unfortunately, so far, there are no established scales to assess the individual thrombotic risk in neurosurgical patients and in particular in these cases that are neurocritically ill. Older age, a history of VTE, obesity, lower extremity motor deficit, or malignant cerebral tumours were identified as specific risk factors for VTE, but, on the other hand, are frequent in neurocritically ill patients.[20]

The second relevant finding of our study was that therapeutic anticoagulation in patients with space-occupying brain infarction and DC was reasonable. The optimal time point to start therapeutic anticoagulation in patients with space-occupying brain infarction and DC is not well defined. Based on an expert consensus, it was suggested to (re)initiate oral anticoagulation 2–4 weeks after space-occupying brain infarction in patients at a high thromboembolic risk.[13] An earlier (re)initiation should critically appraise the individual risk of bleeding and consider risk factors like acute PE or DVT.[13] In a recent multinational randomised clinical trial (Early vs Later Anticoagulation for Stroke With Atrial Fibrillation), early treatment (initiation at days 6–7) with direct oral anticoagulants was not associated with a higher rate of adverse events, especially symptomatic ICH, compared with late treatment (initiation at days 12–14), in patients with atrial fibrillation and major ischaemic stroke.[21] However, major ischaemic stroke was defined as a lesion 'involving the entire middle or anterior cerebral artery territory or lesion >1.5 cm in the posterior circulation'; thus, it is not clear, how many of the patients in the major ischaemic stroke group had a space-occupying brain infarction or at least an infarction of the entire MCA territory. Initiating therapeutic anticoagulation about 2 weeks after space-occupying brain infarction also seemed to be safe with worsening of haemorrhagic transformation in only 6% of patients and clinical deterioration in only 4% of patients in a retrospective single-centre study.[22] Thus, when only considering the infarct size, commencing therapeutic anticoagulation as early as 7 days after stroke onset in patients with space-occupying brain infarction seems to be reasonable. Another concern might be the assumed increased bleeding risk after the preceding decompressive surgery with removal of a large bone flap. In patients with malignant cerebral venous sinus thrombosis (CVST) undergoing DC, therapeutic anticoagulation was not stopped in 41% (11/27) of patients before surgery, and complications during surgery occurred in only 13% (4/31) of patients.[23] Intracranial rebleeding after surgery was reported in 16 of 31 cases (52%), however, it was not clear, whether the rebleeding was related to the malignant CVST, since more than half of the patients also had already a progression of the intracranial bleeding even before surgery.[23] In the Decompressive Surgery for Patients With Cerebral Venous Thrombosis, Part 2, a prospective, international cohort study in patients with malignant CVST and DC, 87% of patients were anticoagulated with heparin, and a new intracranial bleeding occurred in 22% of patients between surgery and discharge.[24] Thus, therapeutic anticoagulation after DC seems not to be associated with a severely increased intracranial bleeding risk.

Based on the findings in our study and the considerations above, in patients with space-occupying brain infarction thromboprophylaxis should be started early, that is, on admission with IPC and LMWH. In addition, whenever possible, thromboprophylactic measures should include passive and active mobilisation and occupational therapy. In case of a VTE, therapeutic anticoagulation with UFH and a targeted aPTT of 50–60 s appears to be feasible.

This study has some limitations. There was no routine screening for VTEs. A routine screening would probably have led to the detection of more VTEs, and consequently, to more patients with therapeutic anticoagulation. Moreover, the clinical significance of VTEs, and in particular of DVT, in patients with space-occupying brain infarction and DC is still unclear. The discrepancy in the frequency of VTEs between our and previous studies[4 8] suggests that clinically inapparent VTEs might be not that relevant for the patient's outcomes. On the other hand, in a meta-analysis of individual patient data, 27% of patients with space-occupying brain infarction and DC were dead after 6 months.[25] However, reasons for death were not reported, and it is speculative, whether patients died because of herniation, withdrawal of life-sustaining therapy, or because of complications like PE.

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