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Original Article

Incidence and Risk Factors for Venous Thromboembolism Following Craniotomy for Intracranial Tumors: A Cohort Study

Abstract

Context: Venous thromboembolism (VTE) is a devastating complication of intracranial tumor surgery. The present study helps identify patients at the greatest risk of developing VTE. **Aims:** The aim of the study was to evaluate the incidence of and risk factors for VTE following craniotomy for intracranial tumors. **Setting and Designs:** This was a retrospective cohort study. **Methods:** Data from the institutional database (between January 2017 and December 2018) were reviewed. Consecutive patients with intracranial tumors who underwent craniotomy were included. **Statistical Analysis Used:** Patient characteristics were reported as descriptive data, and factors associated with VTE development were analyzed by the Cox regression model. **Results:** The study identified 177 patients. The incidence of VTE was 10.2% (deep-vein thrombosis [DVT], 8.5%; pulmonary embolism [PE] 1.7%; and simultaneous DVT and PE, 1.7%). In univariate analysis, VTE development was associated with diabetes mellitus (DM), operative duration of >420 min, blood transfusion, and new-onset postoperative motor deficits. DM and new-onset postoperative motor deficits were statistically significant factors in multivariable analysis, with hazard ratios of 4.52 (95% confidence interval [CI] = 1.38–14.82) and 3.46 (95% CI = 1.17–10.23), respectively. **Conclusions:** Postcraniotomy VTE was detected in 10.2% of patients with intracranial tumors. Risk factors for VTE included DM and new-onset postoperative motor deficits. Hence, intracranial tumor patients with these risk factors are the most likely to require VTE prophylaxis with an anticoagulant.

Keywords: *Craniotomy, diabetes mellitus, intracranial tumor, motor deficit, venous thromboembolism*

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Introduction

Venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a common postoperative complication.[1] It increases the economic burden[2] and leads to patient morbidity and mortality.[3,4] The pathophysiology of VTE – known as the Virchow's triad – involves immobilization, hypercoagulable state, and endothelial injury. Therefore, neurosurgery patients, particularly those with brain tumors, are at a high risk of developing VTE due to many reasons, such as muscle weakness, pro-coagulation factor secretion by tumor cells, and vascular injury following surgery.[5,6]

There has been extensive research on VTE in neurosurgery over the past two decades.[7] In a previous study, hospitalized patients with brain tumors, specifically those treated with surgery, showed a high incidence of VTE.[8] Recently, Rinaldo *et al.* reported a VTE incidence of 0.5%–42.6% from their literature review.[9] VTE development is associated with a number of factors related to patient characteristics, tumor characteristics, and treatment.[6] Therefore, recent VTE guidelines have classified brain tumor patients requiring anticoagulants for VTE prophylaxis into the high-risk group.[10-12] Although these strategies decrease VTE incidence, they increase the risk of intracranial bleeding complications.[13-15]

However, the studies referenced in the guidelines were limited to specific tumors, such as gliomas, used multiple screening tools, and lacked screening protocols for asymptomatic patients.[10,12] The real questions are "Are all patients undergoing brain tumor surgery at a high risk of developing VTE?" and "Do all such high-risk patients require VTE prophylaxis

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with an anticoagulant?" These questions warrant research, and their answers will help neurosurgeons to prescribe anticoagulants without hesitation.

To this end, we aimed to investigate the incidence of VTE in patients undergoing craniotomy for intracranial tumors and to identify the risk factors for VTE in our institution. Our data will help the surgeon to identify high-risk patients eligible to undergo pharmacological VTE prophylaxis.

Methods

Patients

This study was a retrospective review of the cohort database of patients who underwent elective craniotomy for intracranial tumors at Songklanagarind Hospital – a university hospital in Southern Thailand – between January 2017 and December 2018. We included all patients who were 15 years of age or older and presented a pathological diagnosis of intracranial tumors. Patients who underwent stereotactic tumor biopsy or trans-sphenoidal procedures were excluded from the study because they showed better postoperative recovery and earlier discharge than patients who underwent craniotomy.[9] Patients with history and preoperative VTE diagnosed were also excluded.

The database was extensively reviewed, and all patients' data were de-identified. The following parameters were recorded: sex, age, comorbidities, concurrent medications (steroids, antiepileptic drugs, or antiplatelet agents); body mass index (BMI), a history of tumor recurrence, previous radiotherapy or chemotherapy, type of neurosurgical procedure, operative time, estimated blood loss, and the use of blood products. Overweight was defined as BMI ≥23.0 kg/m^2 according to the criteria for Asian patients.[16] We classified patients' ambulation on the basis of their ability to walk as independent when they were able to walk by themselves and dependent when they could not walk by themselves or required walking assistance devices. The overall performance status was evaluated by the Karnofsky Performance Scale (KPS). New-onset neurological deficits as motor deficits were recorded.

Venous thromboembolism screening, prophylaxis, and treatment

VTE is defined as DVT at lower limbs and/or PE.[11] All patients undergoing craniotomy for intracranial tumors were screened for DVT via compression ultrasonography (USG) of both the legs in the postoperative period. Experienced radiologists performed the screening. If the USG results were negative, subsequent USG was performed weekly until discharge. We do not have a screening protocol for PE, and screening was performed when PE was clinically suspected on the basis of unexplained hypoxemia or cardiac arrest. In such cases, chest computed tomography angiography (CTA) was performed to confirm the PE diagnosis. In the outpatient clinic, only those patients with clinically suspected VTE were evaluated via USG or CTA.

For VTE prophylaxis, all patients were weaned mechanical ventilators and were extubated early and mobilized as early as possible. A rehabilitation program was initiated if necessary. Mechanical prophylaxis via pneumatic calf compression, which is not routinely used, was applied at the attending neurosurgeon's discretion. No patient in this study received prophylaxis with anticoagulants due to the lack of experience of surgeons and concerns of intracerebral hemorrhage complications.

We consulted a vascular surgeon for further management of DVT patients and chest physicians or cardiothoracic surgeons for the management of PE patients. The VTE management depended on consulted physician's decisions. The choice of treatment for VTE patients was reviewed.

Statistical analysis

Patient characteristics were reported as descriptive statistics including frequencies, percentages, means with standard deviations (SDs) for parametric data, and medians with ranges for continuous nonparametric data. VTE-free possibilities were evaluated by survival curve analysis using the Kaplan–Meier (KM) method, and Cox proportional hazards regression analysis was used to identify univariable and multivariable factors associated with VTE. Variables associated with VTE with $P \leq 0.05$ in univariable analysis were included in the multivariable analysis using the backward stepwise method. The desired power was set at 80%, and the alpha level for statistical significance using two-sided tests was set at 0.05. Statistical analyses were performed using R version 3.4.0 (R Foundation, Vienna, Austria). The ethical committee of the institute approved this research (REC. 61-252-10-1).

Results

Patient characteristic, pathology, and surgical outcomes

We included 180 patients who met the study criteria; we excluded three patients with a history of prior admission VTE, but preoperative VTE symptomatic patient was not detected. We included the remaining 177 patients in the statistical analysis. Majority of the patients were females (54.2%), and the mean patient age was 50.4 years (SD, 13.8 years). Overweight was the most common comorbidity (58.2%), followed by hypertension (26.0%), dyslipidemia (18.1%), and diabetes mellitus (DM; 13.0%). Majority of the patients (75.7%) were of the physical status class 3 according to the American Society of Anesthesiologists classification. No moribund cases were operated in the elective setting during the study period. We encountered 13% of recurrent tumor patients with a history of irradiation (12.4%) and chemotherapy (7.9%). Majority of the patients were physically active with an independent status in the preoperative period (70.1%), and the median KPS was 60 (range, 30–80). However, 14.7% of the patients presented with altered consciousness. Perioperative steroids and prophylactic antiepileptic drugs were administered to 91.5% and 81.9% of the patients, respectively [Table 1].

Table 1: Baseline characteristics of brain tumor patients (*n*=177)

Factor	*n* (%)
Gender	
Male	81 (45.8)
Female	96 (54.2)
Mean of age (year)±SD (range)	50.4±13.8 (15-86)
Underlying disease	
Hypertension	46 (26.0)
Dyslipidemia	32 (18.1)
DM	23 (13.0)
Pulmonary diseases	5 (2.8)
Kidney diseases	4 (2.3)
Cardiac diseases	3 (1.7)
CVA	1 (0.6)
Other cancer	20 (11.3)
BMI (kg/m^2)	
<18.5	17 (9.6)
18.5-22.9	57 (32.2)
≥23.0	103 (58.2)
ASA classification	
2	36 (20.3)
3	134 (75.7)
4	7 (4.0)
Recurrence tumors	23 (13.0)
Prior RT	22 (12.4)
Prior CMT	14 (7.9)
Antiplatelet use	7 (4.0)
Steroid use	162 (91.5)
Antiepileptic drug use	145 (81.9)
Smoking	49 (27.7)
Preoperative ambulation	
Independent	124 (70.1)
Dependent	53 (29.9)
Mean operative time (min)±SD (range)	428.6±63.5 (145-1005)
Location of craniotomy	
Supratentorial	145 (81.9)
Infratentorial	32 (18.1)
Mean blood loss (ml)±SD (range)	872.6±1290.3 (50-11,000)
PRC transfusion	94 (53.1)
FFP transfusion	87 (49.2)
Platelet transfusion	25 (14.1)
New-onset postoperative motor deficits	42 (23.7)
Postoperative ambulation	
Death	6 (3.4)
Independent	101 (57.1)
Dependent	70 (39.5)

SD – Standard deviation; CDV – Cardiovascular diseases; DM – Diabetes mellitus; BMI – Body mass index; ASA – American Society of Anesthesiologists; RT – Radiation therapy; CMT – Chemotherapy; PRC – Packed red blood cell; FFP – Fresh frozen plasma

Operative time was defined as the time from anesthesia induction to the completion of surgery. The mean operative time was 428.6 min (SD, 163.5 min). The mean estimated blood loss was 872.6 mL (SD, 1290.3 mL), and 63.3% of the patients required blood transfusion. The requirement of perioperative transfusion was determined by the attending anesthesiologist and neurosurgeon. The most common transfusion type was packed red blood cell (PRC) transfusion (53.1%), followed by plasma transfusion (49.2%), and only 14.1% of the patients required platelet transfusion. The median length of hospital stay was 12 days (range, 2–281 days). At discharge, 42 (23.7%) patients showed new-onset postoperative motor deficits. The mortality rate was 3.4%, and 101 (57.1%) patients showed independent ambulation. The postoperative and preoperative KPS was the same (median KPS, 60; range, 0–80).

All tumors were pathologically examined. The supratentorial region was the most common location (81.9%); however, the percentages of intra- and extra-axial tumors were comparable (49.7% and 50.3%, respectively). Meningioma was the most common pathology (36.7%), followed by glioblastoma (14.7%) and metastasis (13.0%). Two patients with pituitary adenomas underwent pterional craniotomy due to the large size of the tumor and its suprasellar extension [Table 2].

Incidence, prophylaxis, and management of venous thromboembolism

Leg USG for screening was performed in all patients. VTE occurred in 18 (10.2%) patients, including 12 (6.8%) with DVT, 3 (1.7%) with PE, and 3 (1.7%) with both DVT and PE. Mechanical prophylaxis with Intermittent pneumatic calf compression (IPC) was used postoperatively in 44 (24.9%) patients. The most common location of leg DVT is proximal leg veins, which found in ten patients (six patients in the common femoral vein and four patients in the superficial femoral vein). Distal leg DVT, popliteal vein, was detected in two patients in DVT alone patients and three patients with simultaneous DVT and PE patients. All PE patients were detected in both the lungs. The most common location of PE is the main pulmonary artery for four patients.

The clinical presentation of VTE depended on its location. DVT patients were more frequently asymptomatic than PE patients; only five DVT patients showed leg pain or edema. Only one patient with PE was asymptomatic [Table 3]. The median times of VTE, PE, and DVT diagnoses were postoperative days 13.5 (range, 2–52), 10 (range, 2–52), and 13 (range, 2–52), respectively. The mean time of diagnosis was not significantly different between asymptomatic and symptomatic VTE patients (18.3 vs. 23.9 days, $P = 0.503$).

Five DVT patients were treated with an inferior vena cava (IVC) filter and five received low molecular-weight

Table 2: Intracranial tumors pathology in 177 patients undergoing craniotomy

Type of pathology	*n* (%)
Intra-parenchymal lesions	88 (49.7)
Glioblastoma	26 (14.7)
Metastasis	23 (13.0)
Astrocytoma	19 (10.7)
Oligodendroglioma	6 (3.4)
Lymphoma	5 (2.8)
Gliosarcoma	3 (1.7)
Ependymoma	2 (1.1)
Hemangioblastoma	2 (1.1)
Oligoastrocytoma	1 (0.6)
Supratentorial neuroblastoma	1 (0.6)
Extra-parenchymal lesions	89 (50.3)
Meningioma	65 (36.7)
Schwannoma	15 (8.5)
Pituitary adenoma	2 (1.1)
Craniopharyngioma	2 (1.1)
Pineal germ cell tumor	2 (1.1)
Central neurocytoma (lateral ventricle)	1 (0.6)
Hemangiopericytoma	1 (0.6)
Medulloblastoma	1 (0.6)

Table 3: Characteristics of venous thromboembolism patients (*n*=18)

VTE characteristic	*n* (%)
Incidence of VTE	
DVT alone	12 (6.8)
Asymptomatic	7
Symptomatic (leg edema or pain)	5
PE alone	3 (1.7)
Asymptomatic	0
Symptomatic	
Dyspnea or deoxygenation	3
DVT + PE	3 (1.7)
Asymptomatic	1
Symptomatic	
Dyspnea or deoxygenation	1
Cardiac arrest	1

VTE – Venous thromboembolism; PE – Pulmonary embolism; DVT – Deep-vein thrombosis

heparin (LMWH); the symptoms were observed in the remaining patients. One patient with PE developed cardiac arrest but did not receive further treatment as per the relative's decision; two patients received LMWH. Three patients with simultaneous DVT and PE were treated with LMWH and IVC filters.

Risk factors for venous thromboembolism

Figure 1a shows the overall VTE-free probability as a KM curve; the calculated probability did not reach the median of overall probability. VTE-associated factors were DM and new-onset postoperative motor deficits. These two factors were presented in KM curves and log-rank tests, as shown in Figure 1b and c. The results of Cox proportional hazards regression analysis are presented in Table 4. In univariable analysis, DM (hazard ratio [HR] = 4.18, 95% CI = 1.39–12.57; P = 0.011), operative time of ≥420 min (HR = 2.74, 95% CI = 1.01–7.40; P = 0.047), PRC transfusion (HR = 3.46, 95% CI = 1.09–10.96; P = 0.035), fresh frozen plasma transfusion (HR = 2.99, 95% CI = 1.02–8.77; P = 0.047), and new-onset postoperative motor deficit (HR = 3.82, 95% CI = 1.40–10.38; P = 0.009) were associated with an increased risk of VTE development. After applying the Cox regression model with the backward stepwise method to establish significant factors in the univariable analysis, two significant factors were detected in multivariable analysis: DM (HR = 4.52, 95% CI = 1.38–14.82; P = 0.013) and new-onset postoperative motor deficit (HR = 3.46, 95% CI = 1.17–10.23; P = 0.025).

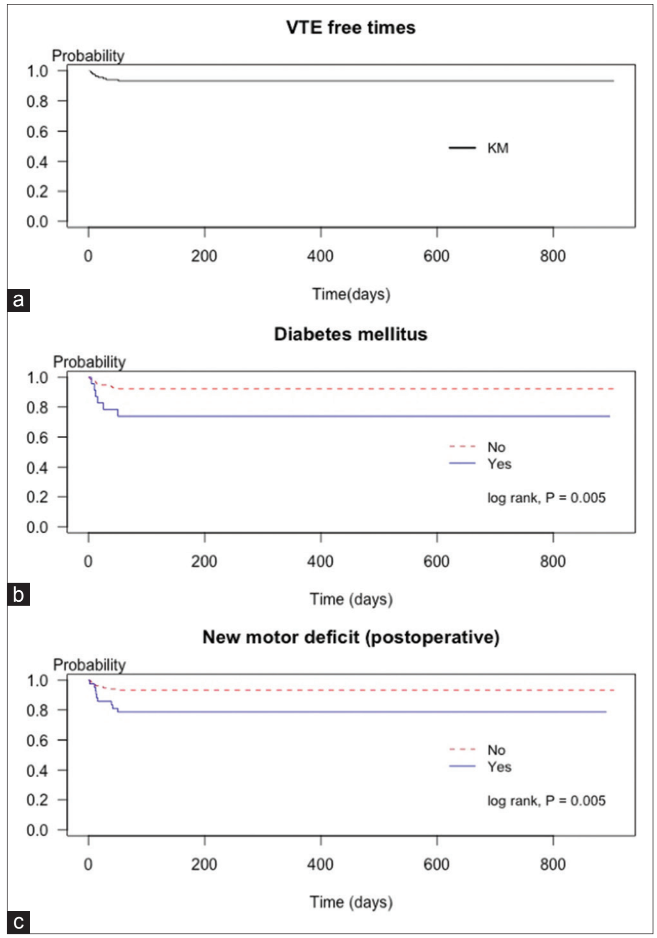

Figure 1: Venous thromboembolism-free probabilities presented by the Kaplan–Meier curve. (a) Kaplan–Meier curve for overall venous thromboembolism-free time. (b) Kaplan–Meier curve presented venous thromboembolism-free probabilities was lower in patients with diabetes mellitus (log-rank test, P = 0.005) and (c) in patients with new postoperative motor deficit (log-rank test, P = 0.005)

Table 4: Factors associated with venous thromboembolism in brain tumor patients by Cox regression analysis

Factors	Univariate analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Patient related factors				
Female	1.06 (0.39-2.83)	0.906		
Age ≥50 years	1.01 (0.38-2.69)	0.986		
Hypertension	1.49 (0.52-4.22)	0.456		
DM	4.18 (1.39-12.57)	0.011	4.52 (1.38-14.82)	0.013
Dyslipidemia	1.34 (0.41-4.37)	0.631		
BMI ≥23.0 (kg/m^2)	1.50 (0.53-4.18)	0.444		
ASA Class 4	1.41 (0.19-10.56)	0.741		
Recurrent tumor	0.82 (0.19-3.58)	0.795		
Antiplatelet use	1.50 (0.17-13.21)	0.715		
Steroid use	1.64 (0.20-13.27)	0.642		
Anti-epileptic drug use	1.86 (0.41-8.53)	0.424		
Smoking	1.35 (0.48-3.82)	0.573		
Preoperative ambulatory dependent	1.56 (0.49-4.98)	0.453		
Treatment-related factors				
Operative time ≥420 mins	2.74 (1.01-7.40)	0.047		
Infratentorial surgery	0.54 (0.12-2.46)	0.424		
EBL ≥900 (mL)	3.08 (1.14-8.30)	0.026		
PRC transfusion	3.46 (1.10-10.96)	0.035		
FFP transfusion	2.99 (1.02-8.77)	0.047		
Platelet transfusion	2.67 (0.86-8.30)	0.089		
New-onset postoperative motor deficits	3.82 (1.40-10.38)	0.009	3.46 (1.17-10.23)	0.025
Postoperative ambulatory dependent	2.27 (0.84-6.17)	0.107		
IPC prophylaxis	2.10 (0.76-5.80)	0.153		
Tumor related factors				
Extra-axial tumor	0.81 (0.30-2.16)	0.674		
Glioblastoma	1.39 (0.51-3.80)	0.523		
Metastasis	0.82 (0.18-3.83)	0.802		
Meningioma	1.18 (0.42-3.31)	0.753		
Schwannoma	1.64 (0.76-5.80)	0.153		

DM – Diabetes mellitus, BMI – Body mass index, ASA – American Society of Anesthesiologists, FFP – Fresh frozen plasma, EBL – Estimated blood loss, PRC – Packed red blood cell, IPC – Intermittent pneumatic compression, CI – Confidence interval

Discussion

In the present study, we investigated the incidence of and risk factors for VTE in patients undergoing craniotomy for intracranial tumors at our institution. In our cohort, all patients were screened with leg USG in the postoperative period. We detected a VTE rate of 10.2% (DVT, 6.8%; PE, 1.7%; and simultaneous DVT and PE, 1.7%).

We searched MEDLINE for studies assessing the incidence of and factors for postcraniotomy VTE. For review, we selected studies that included intracranial tumors, similar to our study. Details of nine studies, including the present study, are summarized in Table 5.[17-24] All studies were retrospective, and there were no previous prospective studies. The incidence of postcraniotomy VTE, DVT, and PE was 3%–23%, 1.9%–21.3%, and 0.8%–3.4%, respectively. The rate of simultaneous DVT and PE was 0%–1.7%; this rate was not reported in two studies.[20,21] A DVT screening protocol was used in three of the 9 (33.3%) studies. However, only the present study screened all patients, and two studies investigated only high-risk patients or those with high D-dimer values.[18,22] The mean rate of DVT was higher in studies that used a screening protocol[18,22] than in studies that did not (11.4% vs. 5.4%).[17,19-21,23,24]

The timing of VTE development is a challenging issue. The exact time of VTE onset is not well established. Clinical studies reported that VTE diagnosis depends on several factors such as patients' symptoms, detection modality, and assessment timing. VTE is usually detected within the first 2 weeks after surgery, ranging from postoperative days 0–64. The reported VTE-associated risk factors include patient-associated factors (female sex,[23] old age,[19,20,24] non-Caucasian ethnicity,[23] prior VTE,[23] hypertension,[19] obesity,[24] KPS <70,[19] and motor deficits[17-19]), tumor-associated factors (supratentorial location[17] and malignant pathology[17,18,23]), and surgery-associated factors (prolonged operative time[20,21] and postoperative infection or sepsis[20,22]). The present study identified DM as a new independent risk factor for VTE.

Table 5: Summarized results of previous studies evaluating incidence and risk factors for postcraniotomy venous thromboembolism in brain tumor patients

Authors and year	Country	Sample size	VTE				VTE detection time (POD)	Image screening protocol (criteria, modality)	Prophylaxis	VTE risk factors*	Remark
			Total (%)	DVT (%)	PE (%)	DVT + PE (%)					
Constantini *et al.*, 1991	Israel	633	4.9	1.9	1.3	1.7	DVT (mean) 9.7±5.0 days PE (mean) 10.0±5.4 days	No	NA	Supratentorial, Malignant glioma, Weakness	Only symptomatic patients
Aishima *et al.*, 2013	Japan	419	5.5	2.9	1.0	1.6	Median 5 days (range 0-47)	Yes (patient with high of abruptly increased D-dimer level, CT with contrast)	ECS + IPC	Malignant tumor, preoperative paresis	Included stereotactic biopsy (10.7%)
Chaichana *et al.*, 2013	USA	4293	3.0	2.0	0.8	0.2	NA	No	IPC + UFH	HGG, HTN, Motor deficit, Age >65, KPS ≤70	Included stereotactic biopsy (7%)
Kimmel *et al.*, 2014	USA	1741	NA	3.2	1.8	NA	DVT (mean) 13.24 days PE (mean) 14.22 days	No	NA	Age >60, Op time >4 h, UTI, Septic shock	
Frisius *et al.*, 2015	Germany	207	NA	7.2	1.9	NA	NA	No	UFH or LMWH + IPC	Operative time >100 min	
Smith *et al.*, 2015	USA	1148	17.1	13.7	3.4	0	Mean 6.1±9.4 days	No	UFH or LMWH	Female, ICU LOS, High-grade tumors, Non-Caucasian, Prior VTE	
Nakano *et al.*, 2018	Japan	61	23.0	21.3	1.7	0	Median 8 days (range 1-64)	Yes (High risk or high D-dimer level, USG)	ECS + IPC	Postoperative infection	
Sender *et al.*, 2018	USA	7376	3.5	2.0	0.9	0.6	Inhospital (median) 6 days (IQR 3-8) Postdischarge (median) 13 days (IQR 6-19)	No	NA	Older age, Higher BMI	
Present study	Thailand	177	10.2	6.8	1.7	1.7	Median 13.5 days (range 2-52)	Yes (all cases, USG)	IPC (24.9%)	DM, New motor deficit	

*The VTE risk factors included only statistically significant in multivariable analysis. DVT – Deep-vein thrombosis; ECS – Elastic compression stocking; ICU – Intensive care unit; IQR – Interuartile range; IPC – Intermittent pneumatic calf compression; KPS – Karnofsky performance status; LMWH – Low molecular-weight heparin; LOS – Length of stay; NA –Not available data; PE – Pulmonary embolism; POD – Postoperative day; UFH – Unfractionated heparin; UTI – Urinary tract infection; VTE – Venous thromboembolism; UGS – Ultrasonography; CT – Computed tomography

Hyperglycemia has been evaluated as a factor associated with a high risk of thrombosis. Laboratory evidence has demonstrated that high serum glucose-induced oxidative stress leads to the malfunction of the endothelial layer, increase in coagulation factor levels, and impairment of fibrinolysis.[25] The results of our study contradict those of a recent population-based study[26] and another meta-analysis,[27] both of which reported a weak but positive or no association between DM and VTE risk. The meta-analysis indicated that the association of DM with VTE might be indirect, reflecting the effect of other VTE risk factors associated with DM, such as obesity.[27] Unfortunately, the association between perioperative blood glucose levels and VTE has not been extensively studied.

VTE preventive strategies can be implemented using many approaches, from encouraging patients to engage in physical activity as early as possible to mechanical and/or pharmacological prophylaxis.[7,28,29] In this study, we mainly used the motivation of patients using both active and passive mobilizations by physical therapists.[30] However, the use of mechanical prophylaxis in our institution is only one-fourth, mainly due to the limited number of devices and lack of funds to purchase compression stockings; these are commonly faced issues in hospitals with limited resources[31] and warrant systematic and policy-based resolution.

The strength of this study is that we screened all patients, achieving the most realistic incidence. However, there are many limitations, such as the retrospective study bias, inconsistent screening periods, and inconsistent IPC usage in patients with or without VTE. Finally, the lack of preoperative screening data made us unable to know the exact time of VTE occurrence.

Conclusions

Patients who underwent craniotomy for brain tumors were examined. Such patients, specifically those with DM and new-onset motor deficits after surgery, are at a high risk of developing VTE. Therefore, such high-risk patients should be prioritized for receiving VTE prophylaxis.

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Conflicts of interest

There are no conflicts of interest.

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