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CLINICAL STUDY

Risk of post-operative venous thromboembolism in patients with meningioma

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Abstract

The surgical resection of meningiomas can be complicated by venous thromboembolism (VTE) in the post-operative period, but the exact incidence of this event is not known. Aim of this study was to assess the occurrence of VTE in patients operated for meningioma who underwent a post-operative clinical and objective screening for VTE. Patients undergoing meningioma resection between 2000 and 2010 who accepted to be investigated for VTE in the post-operative period were included in the study. The screening included daily clinical assessment, pulmonary perfusion scintigraphy (Q-SCAN) on day 2 and venous compression ultrasonography (CUS) of the lower limbs within day 7. The univariate and multivariate statistical analysis of risk factors for VTE included sex, age, presence of comorbidities, pre- and post-operative Karnofsky Performance scale (KPS), post-operative neurological worsening and post-operative walking ability. Two-hundred and seventy-five patients were included in the study. VTE was diagnosed in 82 patients (29.8%). Univariate analysis revealed that age ≥ 65 years, cardiovascular comorbidities, pre- and post-operative KPS < 80/100, post-operative neurological worsening and impaired post-operative walking ability were significantly associated with VTE. Multivariate analysis confirmed only age ≥ 65 years ($p = 0.011$) and post-operative KPS < 80/100 ($p = 0.002$) as independent risk factors for VTE. Patients operated for meningioma have a 30% risk of VTE. Age ≥ 65 years and post-operative KPS < 80 were independent risk factors for VTE.

Keywords Venous thromboembolism · Meningioma · Pulmonary embolism · Deep vein thrombosis

Introduction

Meningiomas are the most common benign brain tumors [1] and are associated with an increased risk of venous thromboembolism (VTE) [2–5]. The exact incidence of VTE in patients operated for meningiomas is unknown. The high variability of data reported in the literature [2–4, 6–8] is due to the different objective methods used to diagnose VTE and to the different design of the studies. In the early 1990s, a prospective study reported a 72% incidence of post-operative VTE when diagnosed with ^{125}I labeled fibrinogen leg scans [2], while in a large retrospective study only 3% of patients developed symptomatic VTE [3].

The diagnosis of VTE is of paramount importance in the postoperative management of neurosurgical patients, since the use of anticoagulant therapy is associated with an increased risk of intracranial hemorrhagic complications [9–12]. The high risk of VTE associated with meningioma prompted us to set up a postoperative screening protocol aimed to detect VTE [13].

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Primary aim of this study was to estimate the risk of VTE in patients operated for meningioma performing pulmonary perfusion scan (Q-SCAN) and lower limb compression ultrasonography (CUS). Secondary aim was the investigation of risk factors for VTE.

Methods

Patients

An investigational protocol for early detection of VTE was applied to patients operated for meningioma at our hospital from May 2000 onwards. This study includes patients of a 10-year period, i.e., operated on until May 2010. Meningioma location was divided in convexity, skull base, and spine. The histological classification of meningiomas was done according to the 2007 World Health Organization (WHO) Classification of brain tumors in grade I, II and III [14]. In those cases operated before 2007, histological diagnosis was reviewed accordingly. Demographic and clinical data were collected. Pre-operative co-morbidities were classified in cardiovascular, respiratory, metabolic and miscellanea (other neoplasms, previous surgeries, psychiatric disorders). Karnofsky Performance Status (KPS) was recorded pre-operatively and at discharge. Post-operative risk factors included the presence of neurological worsening and walking ability .

As common clinical practice, antithrombotic prophylaxis with low molecular weight heparin (LMWH) was administered on a daily basis at a standard dose of 4000 IU subcutaneously starting 24 h after surgery or later if intracranial bleeding was detected at the post-operative brain CT scan. In case of VTE, anti-coagulation was started with LMWH tailored to the single patient's clinico-radiological picture (in most cases 4000 IU twice a day).

The study was approved by the local ethical committee and all patients gave their informed consent to use their data for research purposes.

Diagnosis of VTE

The post-operative follow-up included a daily clinical assessment until patient's discharge, the performance of a Q-SCAN and a CUS.

Clinical assessment

Routine clinical assessment was performed daily and reported in a dedicated database. The assessment included chest evaluation of breathing, subjective questioning for dyspnea and leg examination for symptoms of deep vein thrombosis (DVT). Elastic stockings were used by all patients during surgery and post-operatively. Complications related to any of the treatments were recorded.

Q-SCAN

Q-SCAN was performed the day after surgery (for patients not requiring ICU) or the day after the admission to the neurosurgical ward. Thus, for most patients the Q-SCAN was performed on the 2nd post-operative day because all patients operated for brain tumors by our division spend the first post-operative night in intensive care unit. Q-SCAN was performed immediately after the intravenous injection of a standard dose of 350,000 ^{99m}Tc-labeled aggregates of human albumin (administered activity 111 MBq) in supine patient, after 3–5 respiratory cycles. Images of the lungs were acquired in eight standard projections (matrix 256×256; zoom 1.45; 700 K counts for projection). The presence or absence of pulmonary embolism was established according to modified Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) criteria (PIOPED/PISAPED) [15]. When the Q-SCAN was non-diagnostic (according to PISAPED/PIOPED) [15] for PE and whenever the clinicians judged it necessary, a thoracic angio-CT was performed.

CUS

CUS was performed within the first post-operative week by a vascular surgeon blind about the results of the Q-SCAN.

VTE was diagnosed when patients met one or more of the following criteria: (1) positive Q-SCAN with/without clinical signs and symptoms of VTE; (2) non-diagnostic Q-SCAN but positive angio-CT; (3) positive CUS with/without clinical signs and symptoms of VTE (Fig. 1).

Statistical analysis

Univariate and multivariate statistical analysis were performed to determine the influence of known risk factors for VTE in patients operated for meningioma. The pre-operative risk factors included in the statistical analysis were sex, age (≥ 65 years), presence of comorbidities, KPS and walking ability. A KPS $< 80/100$ was considered as negative prognostic factor. We initially conducted a univariate analysis. Differences in VTE occurrence for independent variables were assessed using Chi square. A p value < 0.05 was considered significant. Subsequently, we performed a multivariable analysis by logistic regression. Candidate risk factors or independent variables that showed a "p" value of less than 0.2 upon univariate analysis were initially considered and introduced into the model at the same time. In order to find the best independent risk factors of VTE, a backward elimination of the least significant predictor in the model was performed, with the stopping rule based on the decrease of

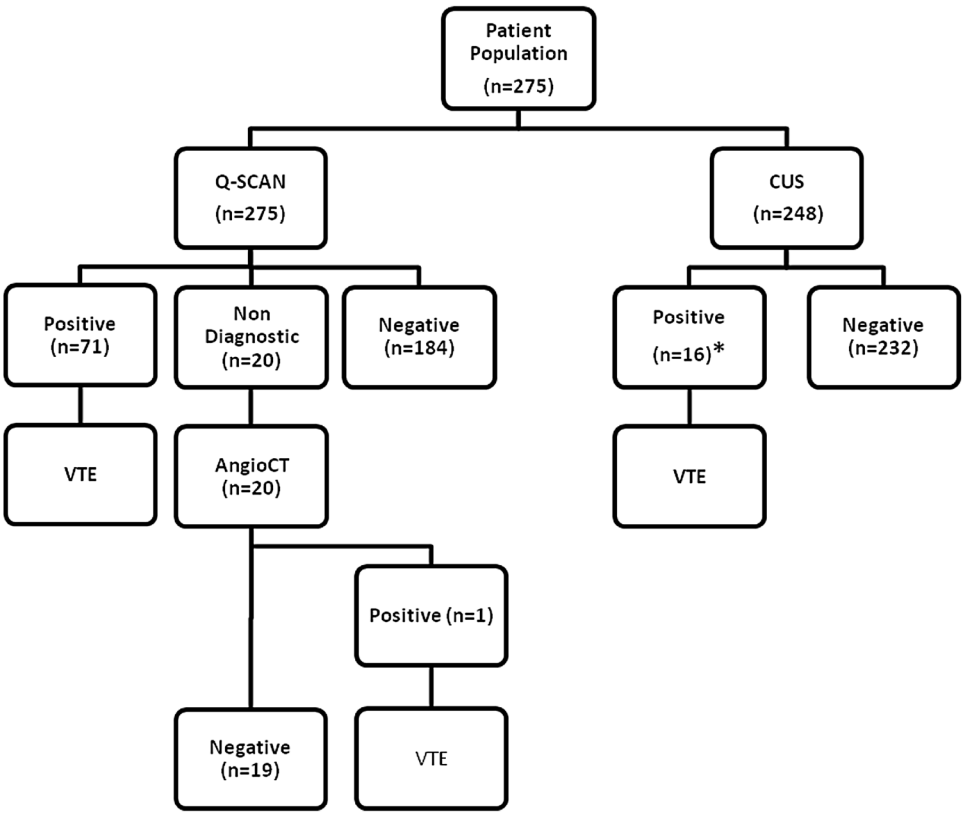

Fig. 1 This figure shows the flow-chart of our study with the positivie findings for VTE. Asterisk represents six patients had also a PE

Akaike's Information Criterion (AIC). Statistical Analyses were performed using R packages, Rcmdr and rms, freely available at the website http://www.r-project.org/.

Results

Of the 306 patients operated for meningioma between 2000 and 2010, 275 (101 men and 174 women) were included in the study. Thirty-one patients did not agree to participate to the study or presented clinical contraindications to perform a Q-SCAN. Hence, the study population was formed by 275 patients. Table 1 shows that most of the patients had pre-operative neurological deficits (65.1%) and comorbidities (overall, 73.5%). Pre-operative and post-operative KPS were similar. A KPS < 80 was recorded in 47 patients (17.1%) pre-operatively and in 59 (21.5%) post-operatively. The most common site of meningiomas was the convexity, followed by the skull base and by the spine. As expected, malignant meningiomas classified as WHO grade III were rare and the majority of patients had grade I meningioma.

Figure 1 shows the investigational protocol for diagnosis of VTE. VTE was diagnosed in 82 patients (29.8%). PE was symptomatic only in eight patients (2.9%) who presented with dyspnea or chest pain. Four other patients (1.5%) developed swelling or pain at a lower limb (Fig. 2). Thus, 12 patients (4.4%) were symptomatic for VTE. Q-SCAN was diagnostic

Table 1 Characteristics of the study population

Patients	275
Median age (min–max)	62 (26–82)
Men/women	101/174
Pre-operative neurological deficits, n (%)	179 (65.1)
Comorbidities, n (%)	
Cardiovascular	117 (42.5)
Respiratory	33 (12)
Metabolic*	81 (29.4)
Miscellanea†	106 (38.5)
Pre-operative KPS ≥ 80, n (%)	228 (82.9)
Post-operative KPS ≥ 80, n (%)	216 (78.5)
Location, n (%)	
Convexity	175 (63.6)
Skull base	80 (29.1)
Spine	20 (7.3)
WHO classification, n (%)	
Grade I	236 (85.8)
Grade II	35 (12.7)
Grade III	4(1.4)

KFS Karnofsky Performance Status

*Diabetes mellitus, obesity, hypercholesterolemia, hypo- or hyperthyroidism, chronic renal or liver disease

†Other neoplasms, previous surgeries, psychiatric disorders

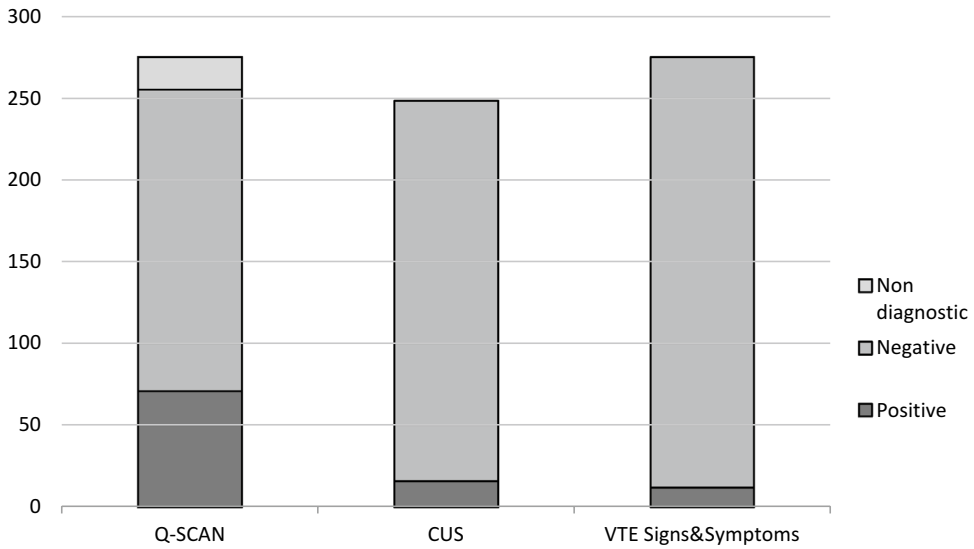

Fig. 2 This graph shows the distribution of patients with positive or negative Q-SCAN, CUS or signs or symptoms. It is interesting that the amount of patients with signs or symptoms is significantly smaller than the number of patients with an occult VTE

of PE in 71 patients (25.8%), non-diagnostic in 20 (7.3%) and negative in 184 (66.9%) (Fig. 2). Fifty-two patients with positive Q-SCAN and 20 with non diagnostic Q-SCAN underwent an angio-CT of the chest that resulted diagnostic for PE in 53 patients (52 with a positive Q-SCAN and 1 with non diagnostic Q-SCAN). Hence, 72 patients (26.2%) developed a PE.

CUS of the lower limbs was performed in 248 patients (90.2%) and was diagnostic for a DVT in 16 (6.4%) (Fig. 2). Six patients (2.4%) had also a positive Q-SCAN, while 10 (4%) experienced an isolated DVT. Two of the four patients symptomatic for DVT had a positive CUS, while the remaining 14 with positive CUS were asymptomatic for DVT.

Seven patients (2.5%) developed intracranial hemorrhagic complications requiring surgery (two epidural hematomas, five intracerebral/surgical cavity hematomas). All bleedings were related to surgery and none occurred after starting antithrombotic prophylaxis. Two patients with intracranial bleeding developed VTE and were subsequently anticoagulated with LMWH.

Univariate statistical analysis of risk factors revealed that age ≥ 65 years, the presence of cardiovascular comorbidities, pre-operative KPS $< 80/100$, post-operative KPS $< 80/100$, post-operative neurological worsening and impaired post-operative walking ability were significantly associated with VTE. Multivariate statistical analysis confirmed only age ≥ 65 years ($p = 0.011$) and post-operative KPS $< 80/100$ ($p = 0.002$) as independent risk factors for VTE (Table 2).

Table 2 Risk factors associated with VTE

	Univariate analysis p value	Multivariate analysis p value
Sex (M vs. F)	0.675	
Age (< vs. > 65 years)	0.008	0.011
Cardiovascular (absent vs. present)	0.016	0.312
Respiratory (absent vs. present)	0.108	
Metabolic (absent vs. present)	0.956	
Miscellanea (absent vs. present)	0.195	
Pre-operative KPS (< vs. > 80)	0.001	
Post-operative KPS (< vs. > 80)	< 0.001	0.002
Neurological worsening (no vs. yes)	0.033	
Post-operative walking ability (worsened vs. stable)	0.005	

KPS Karnofsky Performance Status

Discussion

Malignant tumors are associated with a high risk for VTE which can significantly worsen the prognosis of patients [16, 17]. Meningiomas, benign brain tumors, are associated with a high risk of VTE [2–4] but the exact incidence of such complication is unknown, varying between 3 and 72% when asymptomatic [3, 4, 7] and between 3 and 8% when symptomatic patients are considered [3, 7]. The underlying mechanisms of meningioma-associated VTE remain unclear and include a combination of prothrombotic tumor related factors, patient related factors, iatrogenic factors and factors associated with the inflammatory response [16, 17].

In clinical practice, an active surveillance for VTE is important to avoid such complication that can increase morbidity [13] and mortality [7]. Therefore, we designed a post-operative screening protocol which included a post-operative Q-SCAN and CUS (in addition to common clinical evaluation) in patients operated for meningioma. Q-SCAN was chosen for its high negative (close to 100%) and positive (> 90%) predictive values [15] while angio-CT of the chest was reserved essentially for patients with non diagnostic

Q-SCAN or difficult clinical decisions regarding the introduction of anticoagulation therapy. In the modified PIOPED II study, Sostman et al. demonstrated that the results of perfusion scanning are similar to those of angio-CT, suggesting that ventilation scans are superfluous in most cases [15]. Furthermore the Q-SCAN exposes the patients to lower radiation doses than the angio-CT, it does not impact on renal function and it is also feasible in patients allergic to iodated contrasts [15]. Interestingly, in our study, we found that 23.3% patients operated for meningioma had an asymptomatic PE, with a minority of patients (2.9%) being symptomatic. These data regarding symptomatic patients are similar to those already reported in the literature [3, 17] while the rate of asymptomatic patients with VTE was higher than expected [3, 4, 7]. It remains unclear whether being aware of asymptomatic VTE is clinically important, but it is well known that a post-operative VTE carries a mortality rate which can be as high as 23.1%.

The statistical analysis confirmed that some of the known risk factors for VTE were also present in our cohort [7, 18]: older age (≥ 65 years), the presence of cardiovascular comorbidity and a relatively low pre-operative KPS (< 80/100) were associated with VTE at univariate analysis. The multivariate study of the pre-operative risk factors showed that older age was the only independent risk factor, suggesting that the impact of cardiovascular diseases and low KPS on the risk of VTE was likely dependent on the age of the patients. The impact of age on the development of embolic complications is particularly important because meningiomas are benign tumors which often affect the elderly population and where the indications to surgical resection are mostly debated [13, 19]. Indeed, specific scores to candidate patients for surgery have been developed for this category of patients [13, 19].

The study of post-operative risk factors showed that neurological worsening, impaired post-operative walking ability and low post-operative KPS were associated with the occurrence of VTE at univariate statistical analysis. The multivariate analysis confirmed that only a low post-operative KPS was linked to VTE. Taken together, these results indicate that uncomplicated surgery is extremely important, because the deterioration of neurological and/or clinical conditions (and consequently a decrease of KPS) can influence the occurrence of VTE. In fact, in such cases, Eisenring and colleagues reported a PE related death rate of 23.1% [7], while in a historical cohort of elderly patients with intracranial meningiomas operated in our hospital, the death due to PE occurred in 2.2% of patients [13]. Interestingly, none of the patients included in this study died of PE, suggesting that our investigational protocol was effective in reducing the post-operative death rate due to VTE.

CUS is a non-invasive and widespread technique with 53% sensitivity for DVT in asymptomatic patients and a 95.5% sensitivity for DVT in symptomatic patients [18, 20]. CUS was added to our post-operative screening considering its easy accessibility and supposing that PE was related to DVT. The number of DVTs detected in our series by CUS was relatively low (6.4%) particularly if compared to the high incidence of PE (26.2%). This data is in contrast with the hypothesis that post-operative PE is dependent from DVT occurrence in meningioma patients and suggests that other factors may play a relevant role.

The major limitation of our study was the lack of a pre-operative objective examination (i.e., Q-SCAN and CUS) which would have allowed us to rule out the presence of pre-operative VTE. In fact, in 2011 our research group started a prospective study in which both a pre- and post-operative Q-SCAN were performed in patients with meningioma. Interestingly, the great majority of patients had a negative pre-operative Q-SCAN, indicating that what had been observed in the present study was truly a post-operative phenomenon (data unpublished).

Concerning the diagnosis of PE, Q-SCAN resulted a reliable exam and a non-diagnostic Q-SCAN was associated with a negative angio-CT in all but one patient who underwent both examinations, suggesting that the latter is superfluous in most cases.

The principal drawback of our protocol consisted in the clinical management of asymptomatic patients with VTE. The bleeding risk associated with the use of anticoagulant therapy in patients undergoing a craniotomy for brain tumor resection is approximately 3% [21, 22]. In order to reduce such risk, we decided to tailor anticoagulant treatment on the basis of the clinical and radiological status of patients. The final decision on dose and duration of LMWH therapy was taken together by the neurosurgeon and the hematologist. None of the patients developed intracranial hemorrhagic complications requiring surgery after LMWH introduction and none of them died for VTE complications.

In conclusion, our data suggest that patients operated for meningioma require special care for VTE in the post-operative period, given the 30% risk of VTE. In addition, brain injury of eloquent areas during meningioma surgery does not only affect the post-operative neurological outcome, but also the occurrence of VTE especially in elderly patients. Further studies are needed to clarify the role of patients related factors, tumor factors and molecular factors which may help the physician to better predict the risk of VTE in meningioma patients.

Conclusions

Patients operated for meningioma have a 30% risk of VTE. Age ≥ 65 years and post-operative KPS < 80 were independent risk factors for VTE.

Neurosurgeons and other physicians in charge of meningioma patients should be aware of this risk and encourage preventive measures for VTE (early mobilization, LMWH administration, elastic stockings). Further studies are needed to understand the biological mechanisms causing VTE in patients operated for meningioma.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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