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Clinical Study

Development of venous thromboembolism (VTE) in patients undergoing surgery for brain tumors: Results from a single center over a 10 year period

Timothy R. Smith [a,*], Allan D. Nanney III [b], Rishi R. Lall [b], Randall B. Graham [b], Jamal McClendon Jr. [b], Rohan R. Lall [b], Joseph G. Adel [b], Anaadriana Zakarija [c], David J. Cote [a], James P. Chandler [b]

[a] Department of Neurosurgery, Brigham and Women's Hospital, 15 Francis Street-PBB3, Boston, MA 02115, USA
[b] Department of Neurosurgery, Northwestern University, Chicago, IL, USA
[c] Department of Hematology/Oncology, Northwestern University, Chicago, IL, USA

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ABSTRACT

Patients who undergo craniotomy for brain neoplasms have a high risk of developing venous thromboembolism (VTE), including deep vein thromboses (DVT) and pulmonary emboli (PE). The reasons for this correlation are not fully understood. This retrospective, single-center review aimed to determine the risk factors for VTE in patients who underwent neurosurgical resection of brain tumors at Northwestern University from 1999 to 2010. Our cohort included 1148 patients, 158 (13.7%) of whom were diagnosed with DVT and 38 (3.3%) of whom were diagnosed with PE. A variety of clinical factors were studied to determine predictors of VTE, including sex, ethnicity, medical co-morbidities, surgical positioning, length of hospital stay, tumor location, and tumor histology. Use of post-operative anticoagulants and hemorrhagic complications were also investigated. A prior history of VTE was found to be highly predictive of post-operative DVT (odds ratio [OR] = 7.6, $p = 0.01$), as was the patient's sex (OR = 14.2, $p < 0.001$), ethnicity (OR = 0.5, $p = 0.04$), post-operative intensive care unit days (OR = 0.2, $p = 0.003$), and tumor histology (OR = −0.16, $p = 0.01$). Contrary to reports in the literature, the data collected did not indicate that the administration of post-operative medical prophylaxis for VTE was significant in preventing their formation (OR = −0.14, $p = 0.76$). Hemorrhagic complications were low (2.2%) and resultant neurologic deficit was lower still (0.7%). The study indicates that patients with high-grade primary brain tumors and metastatic lesions should receive aggressive preventative measures in the post-operative period.

1. Introduction

Many studies have indicated that patients who harbor brain tumors have a higher risk of developing venous thromboembolism (VTE) [1–8]. Rates of deep vein thrombosis (DVT) in patients with high-grade brain tumors have been reported to be as high as 20–30%, though their etiology has not been fully explained [9–13]. Proposed mechanisms for the formation of VTE in brain tumor patients include increased local synthesis of tissue factor, as well as limited post-operative mobility, hemiparesis, and genetic predisposition [8,13,14]. In general, spinal or cranial neurosurgical procedures increase the risk of VTE, and rates in patients with brain tumors remain higher than in those without [2,3,15–21].

The development of DVT is associated with significant morbidity and mortality. Sorensen et al. demonstrated that cancer patients with VTE had more than two-fold mortality compared to cancer patients without VTE. Semrad et al. reported a 30% increased risk of death at 2 year follow-up in patients who developed VTE [9,22].

Standard prophylaxis against VTE includes mechanical devices (sequential pneumatic compression devices, compression stockings, etc.), early ambulation, and medical treatment with various preparations of heparin, enoxaparin, or other anticoagulants [23–28]. In patients who have undergone resection of an intracranial lesion, many neurosurgeons remain reluctant to prescribe prophylactic anticoagulants due to the risk of post-operative intracranial hemorrhage [1,3,11,24,29–40].

Despite their prevalence and potential deleterious effects, there remains disagreement over the contributing factors to the development of VTE in brain tumor patients, and also the most effective

* Corresponding author. Tel.: +1 617 525 8371; fax: +1 617 734 8342.
E-mail address: trsmith@partners.org (T.R. Smith).

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Table 1
Baseline characteristics of surgical brain tumor patients evaluated for venous thromboembolic events at a single institution from 1999–2011

Risk factor	Female (n = 608)	Male (n = 538)	Total (n = 1148)
Demographic			
Sex (n, %)	608 (53.0)	538 (47.0)	1148 (100)
Age, years (mean, SD)	53.3 (14.5)	55.2 (14.7)	54.2 (14.6)
18–45 (n, %)	178 (15.6)	134 (11.8)	312 (27.4)
46–55	146 (12.8)	126 (11.1)	272 (23.9)
56–65	153 (12.8)	126 (12.1)	291 (25.5)
>65	125 (11.0)	139 (12.2)	264 (23.2)
Ethnicity (n, %)			
Caucasian	428 (37.3)	385 (33.6)	813 (70.9)
African American	53 (4.6)	46 (4.0)	99 (8.6)
Asian	17 (1.5)	9 (0.8)	26 92.3)
Hispanic	27 (2.4)	33 (2.9)	60 (5.2)
Other	29 (2.5)	31 (2.7)	60 (5.2)
Unknown	53 (4.6)	34 (3.0)	87 (7.6)
BMI, kg/m^2 (mean, SD)	26.9 (6.5)	28.0 (6.3)	27.5 (6.4)
Underweight: <19 (n, %)	31 (5.9)	8 (1.8)	39 (4.0)
Ideal: 19–24.9	198 (20.5)	143 (14.8)	341 (35.2)
Overweight: 25–29.9	153 (15.8)	167 (17.3)	320 (33.1)
Obese: 30–34.9	79 (8.2)	83 (8.6)	162 (16.7)
Morbidly obese: >35	63 (6.5)	43 (4.4)	106 (11.0)
History (n, %)			
Heart disease[a]	205 (17.9)	236 (20.6)	441 (38.5)
Cerebrovascular disease[b]	16 (1.4)	28 (2.4)	44 (3.8)
Venous thromboembolic event[c]	30 (2.6)	32 (2.8)	62 (5.4)
Autoimmune disorder[d]	8 (0.7)	13 (1.1)	21 (1.8)
Pulmonary disease[e]	13 (1.1)	20 (1.7)	33 (2.9)
Peripheral vascular disease[f]	5 (0.4)	7 (0.6)	12 (1.0)
Cancer[g]	199 (17.4)	168 (14.7)	367 (32.0)
Seizure	93 (8.1)	129 (11.3)	222 (19.4)
Smoking (current)	67 (5.0)	60 (5.2)	117 (10.2)
Inherited thrombophilias[h]	2 (0.3)	3 (0.4)	5 (0.7)
Ambulatory	417 (36.3)	378 (32.9)	795 (69.2)
Home medications			
Estrogens	6 (1.2)	0 (0.0)	6 (1.2)
Anticoagulation	48 (7.8)	40 (7.4)	88 (7.5)
Aspirin	16 (2.1)	21 (2.8)	37 (4.9)
Clopidogrel	4 (0.5)	2 (0.3)	6 (0.8)
Aspirin/Dipyridamole	1 (0.1)	1 (0.1)	2 (0.3)
Enoxaparin	4 (0.5)	3 (0.4)	7 (0.9)
Warfarin	11 (1.5)	10 (1.3)	21 (2.8)
Combination	9 (1.2)	2 (0.3)	11 (1.5)

BMI = Body Mass Index, SD = standard deviation.
[a] Heart disease = myocardial infarction, coronary artery disease, congestive heart failure, hypertension, hyperlipidemia.
[b] Cerebrovascular disease = transient ischemic event, cerebrovascular event.
[c] Venous thromboembolic event = deep vein thrombosis, pulmonary embolism.
[d] Autoimmune disorder = systemic lupus erythema, rheumatoid arthritis, connective tissue disease, antiphospholipid disorder, Crohn's disease, ulcerative colitis, vasculitides.
[e] Pulmonary disease = chronic obstructive pulmonary disease/emphysema, pulmonary fibrosis, pulmonary hypertension.
[f] Peripheral vascular disease = venous, arterial.
[g] Cancer = bladder, breast, colon, leukemia, lung, lymphoma, melanoma, ovarian, pancreatic, prostate.
[h] Inherited thrombophilias = antithrombin III, protein C/S, factor V Leiden, prothrombin, hyperhomocysteinemia.

prophylaxis against them. While previous studies have identified blood type, delayed initiation of anticoagulants, and increased age as contributors to post-operative VTE, other patient-specific and peri-operative risk factors have also been implicated [5,41–44]. This single-center, retrospective study aims to determine the risk factors for VTE in patients who have undergone surgical resection of a brain tumor.

2. Methods

This study was a retrospective chart review of consecutive adult patients who underwent surgical resection of a brain tumor at a single institution between January 1999 and December 2010. Patients were excluded if they were younger than 18 years of age at the time of surgery, or were not treated with craniotomy. An extensive chart review was performed and all patient data was de-identified. Parameters collected included: sex, age, ethnicity, body mass index (BMI), length of hospital stay, length of surgery, surgical position, tumor location, tumor histology (as confirmed by our institution's neuro-pathology department), pre-existing co-morbidities, prior anticoagulant use, post-operative VTE prophylaxis, results of upper/lower extremity ultrasounds for DVT, results of diagnostic pulmonary embolism (PE) studies including chest CT scans and ventilation/perfusion scans, and incidence of hemorrhagic complications. A total of 1148 patients fit the above criteria and were included in this study. Each patient's data was compiled, reviewed, and verified for accuracy by multiple independent reviewers.

Univariate (means, standard deviations [SD}), bivariate (odds ratios [OR], *t*-tests, chi-squared, Pearson correlation coefficients) and multivariate regression models (logistic, linear regression) were used to assess relationships among variables of interest. For all study measures, a p value < 0.05 indicated statistical significance. All statistical analyses in this study were performed using