

Venous Thromboembolism in Brain Tumor Patients: A Review of Literature

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Abstract

Venous thromboembolism (VTE) is a relatively common and well-described condition, affecting approximately 1-2% of the general population. VTE can lead to significant morbidity and death via pulmonary embolism (PE). During the post-operative period, VTE occurs at higher rates due to natural thrombotic responses to injury and limited post-operative mobility. In general, rates of post-operative VTE are higher in patients undergoing operations for cranial and spinal lesions than for lesions of other types, a phenomenon that is not fully explained. Several studies have demonstrated that other risk factors for VTE include age, sex, ethnicity, hospital stay length, and coagulation state. Aggressive chemical and mechanical measures for VTE prophylaxis are indicated in the post-operative period to prevent the formation of VTE. Here we review the literature on VTE in brain tumor patients, with a focus on their etiology, diagnosis, treatment, and prophylaxis.

Keywords: Venous thromboembolism; Brain tumor; Deep vein thrombosis; Pulmonary embolism; Thromboprophylaxis

Introduction

Venous thromboemboli (VTE) occur regularly in 1-2% of the general population, with an annual incidence of 1 in 500 [1,2]. VTE can cause death via pulmonary emboli (PE) or significant disability via pain, edema, and post-thrombotic syndrome, a form of venous reflux that occurs secondary to deep vein thrombosis (DVT). VTE occurs at

a higher rate during the post-operative period due to natural thrombotic responses to injury and limited post-operative mobility. Patients harboring brain tumors are more likely to develop VTE than patients who have cancers in other sites (Table 1) [3-24]. Studies have shown that other risk factors for VTE include age, sex, ethnicity, blood type, length of hospital stay, operative duration, and coagulation status [3,6,8-10,14,25-38]. Standard prophylactic measures for VTE include chemical anticoagulation, mechanical prophylaxis, and increased ambulation during the post-operative period [36,39-54].

Cancer Type/Site	Diagnoses/100 Hospitalizations		
	VTE	PE	DVT
Pancreas	4.3	1.2	3.5
Brain	3.5	1.0	2.8
Myeloproliferative, other lymphatic/hematopoetic	2.9	*	2.5
Stomach	2.7	0.7	2.3
Lymphoma, lymphosarcoma, reticulosarcoma	2.5	0.6	2.0
Uterus	2.2	0.5	1.8
Trachea, bronchus, and lung	2.1	0.6	1.6
Esophagus	2.0	*	1.3
Prostate	2.0	0.6	1.6
Rectum, rectosigmoid junction, anus	2.1	0.7	1.4
Kidney	2.0	0.5	1.6
Colon	1.9	0.6	1.4
Ovary	2.0	0.5	1.6

Liver, gallbladder, intra- and extrahepatic ducts	1.8	0.9	1.1
Leukemia	1.7	0.4	1.4
Breast (female)	1.7	0.4	1.3
Cervix	1.6	*	1.4
Bladder	1.0	0.3	0.8
Lip, oral cavity, pharynx	<0.6	*	*
No cancer	1.0	0.3	0.8
^Table adapted from Stein et al. [15], *Insufficient data			

Table 1: Rate of VTE in patients with various types of cancer[^].

This paper seeks to review the relevant and current literature on VTE in brain tumor patients, with particular focus on the risk factors and presenting symptoms of VTE, treatment options for those with VTE, and a review of current prophylactic measures for VTE.

Pathogenesis

Several factors are thought to drive the formation of VTE. Most prominently, these include venous stasis, blood hypercoagulability, and damage to blood vessel walls [2,55]. Unlike typical blood clots, which form as a collection of erythrocytes on a fibrin mesh, VTE develop in several laminar layers of platelets, leukocytes, and fibrin, which surround a nucleus of erythrocytes [2,56]. Venous blood velocity is much slower than arterial blood flow [57]. Combined with the surface of venous valves and the dilated sinuses of the lower extremities, this relative stasis has been proposed as a potential source of VTE [57]. Venous stasis and blood hypercoagulability promote adherence to collection sites, while damage to vessels exposes the collagen-rich interior of vascular walls. Collagen-rich walls have been reported to promote platelet aggregation, which further incites formation of VTE through collection of leukocytes [55,56].

Inflammation is another proposed contributor to the formation of VTE, in large part because of its role in promoting platelet reactivity and increasing circulating complexes like tissue factor (TF) and fibrinogen. Bucek et al. demonstrated that the inflammatory marker C-reactive protein (CRP) increases in patients with DVT and therefore can be considered a potential indicator of the presence of VTE [58]. The endothelium, which expresses pro- and anti-coagulants, as well as vasoconstrictors and vasodilators, plays a prominent role in the development of VTE via inflammation. Wakefield et al. report that when the endothelium is disturbed, either functionally or mechanically, the endothelial surface vasoconstricts and reacts in a prothrombotic fashion. Endothelial cells release pro-thrombotic factors including platelet activating factor (PAF), endothelin-1 (a vasoconstrictor), von Willebrand factor, TF, and plasminogen activator inhibitor [55]. Injury to the endothelium also promotes surface expression of cell adhesion molecules like P-selectin and E-selectin, which promote leukocyte margination and adhesion [55]. The net effect of these inflammatory cascades following injury or disruption of venous vessels promotes VTE development.

VTE in Brain Tumor Patients

Although VTE is relatively common in the general population, it is far more common during the post-operative period [25,27,39-42,51-53]. Proposed explanations for this phenomenon include limited post-operative mobility, which can promote venous stasis, and damage to endothelial tissue, as discussed above.

Several studies have shown that patients harboring brain tumors develop DVT at a higher rate than patients with cancer at other sites or patients undergoing procedures for diseases other than cancer (Table 1) [18,20,59]. Day et al. recently reported a VTE rate of 1.2% for lower extremity arthroplasties, and only 0.53% for shoulder arthroplasties [60]. In a study of patients undergoing operations for lung cancer, on the other hand, Christensen et al. reported a mean risk of 2.0% [61]. Stein et al. report the rate of VTE in brain cancer patients, on the other hand, to be 3.5 diagnoses per 100 hospitalizations [15]. In a separate study of more than 1,000 brain tumor patients, the rate of VTE was 19.4%, though this may be artificially elevated in part due to more aggressive surveillance for DVT and PE.17 In an investigation of site-specific cancer and its relation to VTE formation, Petterson et al. found that brain cancer resulted in one of the highest rates of VTE formation, even after adjusting for complicating factors like age and sex [23].

Many mechanisms have been proposed for the increased rate of VTE in patients with cancer. Several studies have investigated circulating microparticles (MP) in the blood, which originate from cancer cells and often express TF. In 2011, Sartori et al. studied the procoagulant activity of circulating MPs in patients harboring glioblastoma multiforme (GBM). They found that MP activity levels increased in 63.6% of 61 patients who underwent resection of GBM, a statistically significant association ($\chi^2=4.93$, $p=0.026$) [62]. In 2004, Browd et al. demonstrated that DVT formation in patients undergoing neurosurgery has been reported as high as 25%, with mortality rates from PE ranging from 9 to 50% [63]. A study by Khorana et al. of patients with pancreatic cancer further indicated that increased plasma TF—a physiologic initiator of coagulation—is correlated with development of VTE in the post-operative period [64]. The authors also suggest that cancer cells are a potential source of circulating TF, which could be an explanation for the increased rate of VTE in cancer patients [65]. Not all cancers produce these procoagulant effects equally, however, which leads to the disparity in VTE rate between tumors of the brain and cancers of other sites. For example, studies have shown that high-grade tumors of the brain result in a higher

concentration of TF, with an associated higher rate of VTE development [62]. A study of 1000 patients undergoing operations for brain tumors showed a strong correlation between higher tumor grade and DVT development (Table 2) [14,17].

Tumor Type	DVT+/Total Patients (%)
Metastasis	44/185 (23.8)
High Grade Glioma	53/248 (21.4)
Low Grade Glioma	5/28 (17.6)
Meningioma	16/196 (8.2)
High Grade Oligodendroglioma	3/15 (20.0)
Low Grade Oligodendroglioma	2/16 (12.5)
Mixed	3/9 (33.3)
Sarcoma	0/3 (0.0)
Schwanomma	4/22 (18.2)
Acoustic Neuroma	0/1 (0.0)
Medulloblastoma	0/6 (0.0)
Lymphoma	8/27 (29.6)
Pituitary Adenoma	0/10 (0.0)
Ependymoma	0/6 (0.0)
Hemangiopericytoma	1/4(25.0)
Choroid	0/3 (0.0)
Hemangioblastoma	2/9 (22.2)
Other	15/88 (17.0)

*Table adapted from Smith et al. [17].

Table 2: DVT development by brain tumor type*.

Risk Factors

Risk factors for VTE are well-described in the literature, and many studies have examined a range of variables for their effect on rate of VTE development (Table 3) [66]. The most commonly reported risk factor for VTE is age. In 1994, Kniffin et al. report that the annual incidence rates per 1000 from age 65 to 69 is 1.3 for PE and 1.8 for DVT. The incidence rates increased steadily with age: at 85 to 89, the annual incidence rates were 2.8 and 3.1, respectively [29]. In 2004, a study by Stein et al. corroborated these results, demonstrating that patients aged 30 to 39 years have a two-fold higher risk of DVT or PE compared to younger patients, while patients 70 years or older have an 18- to 28-fold increase in risk of DVT or PE than those aged 20 to 29 years [67].

A separate study by Geerts et al. suggested that age higher than 40 years is an important risk factor for development of VTE [68]. Other risk factors for the development of VTE that have been explored in the literature include sex, ethnicity post-operative ICU days, anti-coagulation state, and blood type [15,17,65].

Risk Factor	Univariate OR (95% ci)^	Multivariate OR (95% ci)^
Age		1.03 (1.02-1.03)
Weight		1.01 (1.01-1.01)
CNS Tumor	3.69 (3.00-4.52)	2.24 (1.71-2.94)
Sex	0.84 (0.72-0.98)	
Hemiparesis prior to surgery	4.25 (3.27-5.52)	1.80 (1.32-2.45)
Paraparesis	2.56 (1.78-3.69)	
Quadraparesis	3.78 (2.00-7.17)	
Tobacco Use	0.60 (0.48-0.73)	

*Table adapted from Rolston et al. [62], ^All OR are statistically significant

Table 3: Risk factors for development of post-operative VTE in neurosurgical patients*.

In the case of patients harboring brain tumors, several risk factors for VTE development are of particular concern. Many patients undergoing operations for tumors of the central nervous system suffer hemi-, para-, or quadraparesis, either as a result of their tumor pre-operatively, or as a post-operative complication, which can promote DVT development by limiting ambulation [66]. Studies have also demonstrated that patients on steroids have a higher rate of VTE—often, steroids are prescribed as a post-operative regimen after transcranial operations. Patients who have undergone chemotherapy or radiation—both common treatments for many brain lesions—also develop VTE at a much higher rate than those who have not [66]. A particularly unique risk factor for patients harboring brain tumors is the tumor itself, which, as discussed above, can act in a prothrombotic fashion that differs by tumor histology [17]. Studies have shown that tumors of a high grade (e.g., high-grade gliomas and oligodendrogliomas) are more likely to result in post-operative VTE than tumors of a lower grade (e.g., meningioma, pituitary adenoma) [14,17].

Presenting Signs and Symptoms

Patients with VTE present with a variety of signs and symptoms. These vary based on the location of VTE (e.g., PE vs. DVT) but help the practitioner establish the diagnosis and localize the thrombosis. In the case of DVT, patients often present with pain and edema of the affected extremity [69-71]. Other symptoms include tenderness of the extremity, sometimes with a palpable mass, skin blanching, and excessive warmth or redness in the extremity [16,31,43,69]. In the case of PE, common presenting signs and symptoms include dyspnea, pleuritic pain, cough, hemoptysis, and palpitation [69,72]. VTE (especially DVT) is occasionally found in patients that are asymptomatic.

When a patient presents with clinical signs and symptoms of VTE, final diagnosis is often made radiographically. For DVT, upper/lower extremity ultrasound is often sufficient to locate and image the embolus [42,72]. In the case of PE, more common radiographic techniques include chest CT scans and V/Q scans [14,26,31,71].

Prophylaxis

Chemical

Chemical prophylaxis for VTE is extremely common, and most often involves the administration of low-dose or low molecular weight heparin, or enoxaparin. In a meta-analysis of general surgical patients, Clagett et al. demonstrated that the administration of low-dose heparin was effective in preventing the formation of DVT [32,73]. Other studies, however, have demonstrated that sometimes heparin is ineffective in preventing VTE [74].

In neurosurgical patients, one of the primary concerns after the administration of heparin or other anti-coagulants is the risk of intracranial hemorrhage. Patients undergoing transcranial operations for tumors or vascular lesions are already at an increased risk for hemorrhage, and the addition of anti-coagulant medication has been proposed as a potential risk factor for higher rates of hemorrhage among neurosurgical patients. Data on this association have been mixed. Some studies have demonstrated an increased rate of intracranial hemorrhage when VTE chemoprophylaxis is initiated pre-operatively [45]. Other studies have demonstrated no statistically significant association between the two [75-78].

Mechanical

Intermittent pneumatic compression (IPC) and compression stockings are the most common forms of mechanical prophylaxis for VTE [79]. In a systematic meta-analysis, Vanek et al. demonstrated that IPC decreased the risk of DVT by 62% compared to a placebo, 47% compared to high-pressure stockings, and 48% compared to low molecular weight heparin [80]. In a randomized trial of neurosurgery patients, Turpie et al. corroborated this data by reporting the incidence of DVT at 8.8% in patients using high-pressure stockings, 9% in patients using IPC, and 19.8% in an untreated control group [81]. Kurtoglu et al. similarly reported that IPC was as effective as low molecular weight heparin in DVT prophylaxis following head and spinal trauma [32]. Often, IPC and compression stockings are combined for use in a single patient. Although effective at preventing DVT, Vanek et al. report that IPC and compression stockings have no effect on the rate of PE formation [80].

Because paresis and limited post-operative mobility are often reported as risk factors for the development of DVT, post-operative ambulation is encouraged for prophylactic purposes. Intervention with physical therapy for patients who are not ambulatory is often employed as an additional prophylactic. Post-operative ambulation and exercise can help prevent venous stasis, which contributes to the development of VTE as described above [30,34,39,40,68].

Combined prophylaxis

Because both mechanical and chemical prophylaxis are effective at reducing the rate of VTE development during the post-operative period, they are frequently prescribed simultaneously as combined prophylaxis. Several studies have compared the effectiveness of chemical anticoagulation with the effectiveness of mechanical prophylaxis [7,32,36,45,52,74,82]. Many of these studies show that combined prophylaxis has a higher effectiveness in preventing VTE without increasing risk to the patient than either method alone (Table 4) [82].

DVT			
Reference	Combination (%)	Compression (%)	Risk Ratio
Agnelli et al. [75]	22/153 (14)	42/154 (27)	0.53 (0.33-0.84)
Dickinson et al. [43]	4/23 (17)	3/22 (14)	1.28 (0.32-5.06)
Nurmohamed et al. [42]	32/241 (13)	49/244 (20)	0.66 (0.44-0.99)
Subtotal	58/417 (14)	94/420 (22)	0.62 (0.46-0.84)

*Table adapted from Zareba et al. [78].

Table 4: Effectiveness of compression vs. anticoagulation and compression combined in preventing post-operative VTE after neurosurgery*.

Timing of prophylaxis

Proper timing of prophylaxis for development of VTE in surgical patients remains controversial. Many guidelines have been put forth regarding proper type, timing, and administration of VTE prophylaxis. The American Society of Clinical Oncology (ASCO), in its 2007 guidelines on VTE prophylaxis in patients with cancer, recommends that all patients with cancer undergoing major surgery for malignant disease should be considered for pharmacologic thromboprophylaxis, and endorses low molecular weight heparin as the “preferred agent” for treatment of VTE [83]. Nevertheless, the society’s recommendations remain purposefully open, leaving most of the decision on VTE prophylaxis up to the treatment team based on the clinical details of each particular patient. In a 2015 update to the 2007 guidelines, the ASCO provided similar recommendations, expanding their guidelines to include stronger language regarding the necessity of VTE prophylaxis in most hospitalized cancer patients. The American College of Chest Physicians and the Canadian Association of Gastroenterology also lobby for chemoprophylaxis of patients at risk for VTE, but do not provide specific recommendations on the timing, type, or duration of that prophylaxis.

In the case of patients with brain tumors, neurosurgeons are often wary of prescribing pre-operative anticoagulants that may be employed in other types of surgery due to the risk of intracranial hemorrhage intra- or immediately post-op [84]. Intracranial hemorrhage poses a serious risk to the patient’s cognitive and functional outcome, and can lead to re-operations and iatrogenic morbidity. In other disciplines, the administration of pre-operative chemical anti-coagulants remains more generally accepted because of lower danger of complications from intra-operative bleeding. For patients with brain tumors, pre-operative anticoagulation is generally discouraged [5,7,17,30,47,49,52,53].

For the same reason, neurosurgeons are often overly cautious of prescribing chemical anticoagulants during the post-operative period, particularly in the case of brain tumor patients. Several studies have shown that the rates of post-operative hemorrhage are higher in patients undergoing resection of a brain tumor than those in patients undergoing trauma or spinal neurosurgery [32,52,76,77]. Carman et al. surveyed American neurosurgeons and reported that, generally, they underestimate the risk of DVT after brain surgery, and tend to avoid the use of chemoprophylaxis [84]. They remain committed to VTE prophylaxis via mechanical means, however, almost universally

providing patients with some form of mechanical prophylaxis (e.g., ICP). This mechanical prophylaxis is often used without combined chemical prophylaxis, however [84]. Despite mounting evidence of both their safety and efficacy, chemical anticoagulants are underprescribed by neurosurgeons during the post-operative period [32,75,77,78,82,84].

Treatment for VTE

There are several methods for treating VTE. The first line of treatment is chemical anticoagulation, usually with heparin [43,55,70,81]. Treatment with heparin often resolves VTE and its associated symptoms. In some cases, however, anticoagulation is contraindicated. Contraindicated patients include patients who are non-ambulatory or comatose. Treatment with anticoagulants in these cases can lead to hemorrhage and associated morbidity and mortality.

When anticoagulants are contraindicated, VTE can be treated endovascularly, most often with filters. VTE filters are placed most frequently in the inferior vena cava (IVC) to prevent a circulating clot from becoming a PE. IVC filters have been shown to be extremely effective in preventing the development of PE and in decreasing the morbidity and mortality of patients known to be harboring VTE of any kind [10,11,32,34].

Conclusion

Although VTE can be common, prevention is possible in brain tumor patients. Post-operative VTE chemoprophylaxis, when prescribed appropriately, is a safe treatment option for patients who are at high risk for VTE (e.g., patients undergoing transcranial operations). Despite this, many neurosurgeons remain wary of prescribing prophylactic doses of anticoagulants during the post-operative period. The rate of VTE development in the post-operative period for brain tumor patients can be significantly decreased by effective use of both chemical and mechanical thromboprophylaxis.

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