Venous Thromboembolism Prophylaxis: Safe, but Still Provocative?

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There have been substantial advances in the management of venous thromboembolism (VTE) over the years.[1] Unanswered questions remain, especially with regards some important patient subgroups.

Primary prophylaxis for VTE in patients with brain tumors, either primary or metastatic, continues to stir discussion in neurosurgery. At the core, the risk of morbidity and mortality from intracranial hemorrhage (ICH) is balanced against that of VTE and associated sequelae. This is further complicated by the lack of evidence investigating the benefits, risks, and long-term outcomes of chemical and nonchemical thromboprophylaxis in brain tumor patients and confounded by the myriad variables our patients harbor—type of tumor and pathology-associated hemorrhage risk, neurologic and functional status, and the risks in pre- and early perioperative episodes of care. Moreover, the collective empirical data neurosurgeons gather in their own practices have always been powerful forces in decision-making. We encounter the use of anticoagulants in many patients we treat (not just tumor), and we commonly handle traumatic hemorrhages in patients on antiplatelet agents (often multiple), low-molecular weight heparin (LMWH), or, with increasing frequency, direct oral anticoagulants (DOACs). The perception of difficult hemostasis—or a hemorrhage after surgery—informs every surgeon's views of this topic.

What continues to fuel discussion is that the risk of VTE in brain tumor patients is high; estimates have ranged from incidences of between 15 and 30% in some reports.[2–4] Some have also suggested a continuous risk in patients with malignant glioma—that per month of survival, there is a 1.5 to 2.0% risk of events.[5] One can generally categorize these as perioperative or not, as the treatment and hemorrhage implications are different. Patients with malignant brain tumors, whether primary or metastatic, are at an even greater risk for developing VTE in the postoperative period owing to diminished mobilization. (Patients with benign tumor, such as meningiomas, are also at calculable risk.) The risk factors for VTE development in brain tumor patients are multifactorial, but the factors can be categorized as patient-specific (age, weight, functional status, paresis, etc.), tumor-related (type of metastasis, glioma subtype, tumor grade, tumor size, *IDH1* status, podoplanin expression, etc.), and treatment-specific (surgery, length of surgery, extent of tumor resection, glucocorticoid use, chemotherapy, radiation, etc.). Each of these risk factors is believed to modulate one or more of the factors that drive formation of VTE—for example, venous stasis, hypercoagulability, and endothelial damage.

The prophylactic methods for VTE are chemical and/or mechanical. Chemical prophylaxis mainly includes unfractionated heparin and LMWH but is beginning to extend to include DOACs that inhibit either factor Xa or thrombin (e.g., dabigatran, apixaban, edoxaban, and rivaroxaban). Mechanical prophylaxis consists of compression stockings, intermittent pneumatic compression, and ambulation/exercise. Mechanical methods are really not controversial in the eyes of most neurosurgeons.

The timing, specific agents, and duration of chemical prophylaxis have not been universally adopted, mainly due to concerns over hemorrhage. A commonly agreed upon principle is that immediate preoperative administration of chemoprophylaxis is often avoided due to demonstrated hemorrhage risk. Mounting literature, in general, has validated early findings from randomized trials where medical prophylaxis using unfractionated heparin or LMWH with compression stockings and/or pneumatic devices showed superiority to mechanical devices alone in prevention of VTE, with small hemorrhage risk.[6,7] Despite strong evidence of the utility of chemical prophylaxis in the prevention of VTE after surgery, its implementation varies by institution and by surgeon even within the same department, and it is very likely underprescribed by neurosurgeons in these patient populations. In a recent review of 1,622 patients, overall rates of VTE were low (3% in 30 days

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after surgery) in a mixed pathology (benign and malignant tumors) postoperative population in an institution with an aggressive postoperative mobilization paradigm, with only select use of chemical prophylaxis. Expectedly, risk factors for VTE development included poor Karnofsky Performance Scale, motor deficits, and prior VTE, among other factors.[8] Other centers have reported similar rates of VTE but with routine use of subcutaneous heparin.[9] It is very likely that the rates of VTE would be reduced further if maximal mechanical means of prevention were combined with proven pharmacologic means.

Overall, the preponderance of evidence suggests that the risk of VTE formation is mitigated by the use of chemoprophylaxis, beginning in the postoperative period. However, recent literature underscores the importance of dose and pathology in the use of enoxaparin in particular. A recent matched, retrospective cohort study assessed the safety of therapeutic as opposed to prophylactic anticoagulation in patients with high-grade glioma, finding that those receiving enoxaparin were more likely to develop a major ICH, compared with those who did not receive anticoagulation (14.7% vs. 2.5%; hazard ratio = 3.37).[10] The literature in patients with metastatic tumors is more sparse but supports the concept that not all patients with central nervous system (CNS) disease are equal and that pathology matters. The rates of ICH in patients treated for VTE with enoxaparin did not differ from a matched series of untreated patients; hemorrhage rates were higher in patients with tumors prone to bleed—melanoma and renal cell carcinoma—but did not differ in treated and untreated patients.[11]

Given the risk of VTE formation in brain tumor patients, there has been an interest in potentially administering long-term chemoprophylaxis to these patients. In the accompanying study,[12] Miranda et al analyzed patients with cancerous brain tumors (primary or metastatic) post hoc from the AVERT trial[13] who were randomized to apixaban 2.5 mg twice daily or placebo with primary endpoints of VTE/pulmonary embolism and safety measures of major bleeding event. Patients on prophylaxis had fewer events and no major bleeding was reported, though the numbers studied were small and notoriously vascular tumors not included. In addition, the complex issues of perioperative management are not addressed given the study design.

The data for postoperative extended-length chemoprophylaxis beyond the hospitalization in patients with brain tumors is scarce and inconclusive and is not generally implemented, acknowledging patient-specific risk factors that may well indicate that it should be continued. The fear of hemorrhage, no matter how low the risk, is the prime driver of neurosurgical behavior in this domain.

In our experience, preventing and treating VTE in patients with brain tumors is done best when vascular medicine specialists, neurosurgeons, and medical oncologists collaborate and communicate seamlessly, because despite our attempts to generalize, our patients often present with individual risk factor profiles, obfuscating a "one-size-fits-all" approach. In general, we have not advocated a policy of performing screening ultrasound or imaging in patients with brain tumors, which undoubtedly increases the reported rates of VTE. Currently, in the postoperative period in patients with glioma or metastatic tumors, we apply mechanical prophylaxis and mobilize aggressively on postoperative day 1. Patients are started on subcutaneous heparin (5,000 U given three times daily) or LMWH (enoxaparin 40 mg once a day) until discharge home and continued if discharged to skilled nursing or acute rehabilitation. No chemical prophylaxis-related hemorrhages have been observed in the practice of the senior author (I.F.D.) in the postoperative setting after craniotomy for tumor resection in a series of over 3,000 patients. In the outpatient setting, we have favored the use of warfarin for the treatment of VTE, exclusively due to its ready reversibility, despite evidence of the superiority of LMWH in patients with cancer. However, should the availability of newer reversal agents for DOACs (e.g., idarucizumab, andexanet alfa) proliferate, this stance will soften in time. As it is, these are often used without our consultation as our patients are managed in different centers by at times nonoverlapping teams, so their increasing use is a reality. The data from Miranda et al are encouraging in this regard.

Myriad questions remain—some of which are raised by Miranda et al—including the paradigm of routine prophylaxis in the outpatient setting and with what agent; the optimal method of *treating* VTE in this patient population; how the exact pathology and the radiographic CNS tumor burden influences this; and the age-old but ongoing questions of how to prevent and treat VTE in the immediate postoperative setting. Whether new anticoagulants in development and their accompanying reversal agents will provide new options remains to be seen.[14,15]

Conflict of Interest
None declared.

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