Risk of intracranial hemorrhage in glioma patients receiving anticoagulant therapy for venous thromboembolism

Ali K. Choucair, M.D., Pamela Silver, B.A., and Victor A. Levin, M.D.

Brain Tumor Research Department, Department of Neurological Surgery, School of Medicine, University of California, San Francisco, California

To determine the risk of intracranial hemorrhage in patients with malignant gliomas who are treated with anticoagulant drugs for late postoperative venous thromboembolism, the authors retrospectively reviewed the computerized data base of all patients with primary brain tumors seen at the University of California, San Francisco, over a 9-year period. Of 915 patients 18 years of age or older who had a pathological diagnosis of malignant glioma and an initial Karnofsky performance scale score of 60% or higher, 36 (4%) developed venous thromboembolism 6 to 246 weeks postoperatively and 22 were treated with anticoagulant drugs. Anticoagulant therapy usually consisted of intravenous heparin for 7 to 10 days, followed for at least 3 to 6 months by either subcutaneous heparin (5000 to 8000 U twice daily) or oral warfarin. All patients were closely monitored to ensure control of hypertension, compliance with therapy, maintenance of prothrombin time within the therapeutic range, and early recognition of adverse side effects. No patient had an intracranial hemorrhage. Thus, anticoagulant agents can be safely administered after intracranial operations for malignant gliomas without increased risk of morbidity or mortality if the patients are carefully monitored according to established guidelines.

Key Words • anticoagulation therapy • glioma • venous thromboembolism • brain neoplasm
which was diagnosed 6 to 246 weeks postoperatively. Ten of these patients died suddenly and 17 received anticoagulant therapy for at least 3 months (range 3 to 30 months). At the time of tumor diagnosis, the Karnofsky score was 70% or higher in 19 patients (70%) (five of whom died suddenly), 50% to 60% in two patients, less than 50% in one patient, and unrecorded in five patients (four of whom died suddenly); 15 patients (56%) were undergoing chemotherapy, six (22%) were receiving both chemotherapy and radiation therapy, and six (22%) had completed their treatment. None of the treated patients had an intracranial hemorrhage.

All 22 patients (61.1%) who received anticoagulant therapy were carefully monitored to ensure that prothrombin time (PT) and partial thromboplastin time (PTT) remained in the therapeutic range. Anticoagulant therapy usually consisted of intravenous heparin for 7 to 10 days, followed by subcutaneous heparin (5000 to 8000 U twice daily) for at least 3 months. The average duration of anticoagulant therapy was 6 months. Three patients in whom computerized tomography (CT) scans showed large enhancing tumors developed recurrent venous thromboembolism and had to take anticoagulant drugs for more than 2.5 years. The PT and PTT were carefully monitored in each case; none of the three patients developed a bleeding complication.

Discussion
Venous thromboembolism has been cited as a postoperative complication in 29% to 43% of patients who undergo neurosurgical procedures. Brisman and Mendell found that 3.5% of all patients with brain tumors had clinical or autopsy evidence of thromboembolism. Ruff and Posner cited a 10% risk of thromboembolism 6 or more weeks after operation for intracranial glioma. In our series of patients with malignant gliomas, more than 95% of whom were treated with chemotherapy and radiation therapy, 4% of patients developed venous thromboembolism more than 6 weeks postoperatively.

Although venous thromboembolism can be treated effectively with anticoagulant drugs, this treatment can predispose the patient to bleeding complications. Intracranial hemorrhage is thought to account for 0.5% to 1.5% of all bleeding events related to the administration of warfarin. The major risk factors for anticoagulant-related intracranial hemorrhage are the patient's noncompliance, trauma, inadequate PT monitoring, and hypertension. Hypertension was present in 67% of patients who had intracranial hemorrhage while receiving anticoagulant therapy in one series and in 80% of patients in another series.

The relationship between brain tumors and intracranial hemorrhage has been the subject of many reviews. Kase stated that hemorrhage occurs in less than 1% of patients with brain tumors, and that tumors were found in 2% to 10% of patients with intracerebral hemorrhage. On the basis of clinical, surgical, and autopsy data, Wakai et al. reported that hemorrhage occurred in 2.3% of nonpituitary brain tumors in patients older than 15 years of age. In the series of Little, et al., 4% of intracranial hemorrhages were due to primary brain tumor and 2% to metastatic disease.

Despite the potential for intracranial bleeding, there is evidence that anticoagulant therapy can be safely administered to patients with malignant gliomas. Ruff and Posner found no significant difference in the incidence of intracranial hemorrhage between patients who received anticoagulant therapy (1.9%) and those who did not (2.2%). In our series, none of the 22 patients who were treated with anticoagulant agents for at least 3 months had an intracranial hemorrhage despite CT evidence of an enhancing tumor in each case. These studies demonstrate that properly administered and carefully monitored anticoagulant therapy for venous thromboembolism does not increase the risk of intracranial hemorrhage in patients with malignant gliomas. Such patients should be counseled by a physician experienced in the use of anticoagulant drugs and should be followed very carefully to ensure control of hypertension, strict patient compliance, close PT monitoring, and early recognition of adverse side effects.

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References

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Address for Dr. Choucair: Marshfield Clinic, Department of Neurology, 1000 North Oak Avenue, Marshfield, Wisconsin.
Address reprint requests to: Ali Choucair, M.D., c/o The Editorial Office, Department of Neurological Surgery, 1360 Ninth Avenue, Suite 210, San Francisco, California 94122.

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