# Thromboembolism in Patients With High-Grade Glioma

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• *Objective*: To identify factors related to increased or decreased risk of thromboembolism (TE) in patients with high-grade glioma.

• *Design*: We performed a retrospective analysis of 64 patients enrolled in two prospective clinical trials of chemotherapy and radiation therapy for newly diagnosed high-grade glioma.

• *Material and Methods*: The 64 patients were 18 years of age or older and had histologically confirmed grade 3 or 4 astrocytoma, mixed astrocytoma-oligodendroglioma, or gliosarcoma. The diagnosis of TE was confirmed by impedance plethysmography, venography, duplex ultrasonography, ventilation-perfusion lung scanning, or pulmonary angiography. For statistical analysis, the study group was divided into those with and those without TE.

• *Results*: TE developed in 18 of the 64 patients (28%). Of the 18 patients, 11 had deep venous thrombosis of a lower extremity, 5 had pulmonary emboli, and 2 had superficial thrombophlebitis. A paretic arm ($P = 0.017$), a paretic leg ($P = 0.026$), or a history of TE before the diagnosis of glioma ($P = 0.076$) was more common in patients with TE than in those without TE. Ten patients in the group without TE were using aspirin preoperatively in comparison with no patient in the TE group ($P = 0.05$). No significant differences were noted in duration of survival (median, 39.4 weeks and 46 weeks for the TE and non-TE groups, respectively). One patient with apparently excessive anticoagulation had a fatal intracerebral hemorrhage.

• *Conclusion*: This study suggests that TE in patients with newly diagnosed high-grade glioma might be associated with a history of TE or with a paretic extremity; however, no evidence of worse survival was noted in the TE group. Treatment with heparin followed by warfarin sodium was associated with infrequent bleeding complications. An intriguing finding was that the use of aspirin before operation was associated with a decreased risk of TE. Thus, a prospective study with use of aspirin in patients with high-grade glioma at risk for TE would be reasonable.

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DVT = deep venous thrombosis; TE = thromboembolism

Thromboembolism (TE) is a well-known complication in neurosurgical patients and in patients with brain tumors. Estimates of postoperative TE range from 25 to 33% in general surgical patients and from 45 to 70% in patients who have undergone total hip replacement.[1] The incidence of deep venous thrombosis (DVT) and pulmonary embolism in neurosurgical patients is similar to that in high-risk surgical patients. The incidence of DVT ranges from 9 to 50% and of fatal pulmonary embolism from 1.5 to 3%.[2] The incidence of TE in patients with glioma varies from 36.7% in patients who receive no antithrombotic prophylaxis to 10% in those who receive intermittent pneumatic compression to the calves.[3] The current study was undertaken to explore, in patients with high-grade glioma, the associations between TE and factors potentially related to an increased or decreased risk of occurrence of TE.

## MATERIAL AND METHODS

***Study Subjects.***—In this retrospective study, we reviewed the records of 64 patients from the Mayo Clinic who participated in two prospective trials of single-agent nitrosourea chemotherapy and radiation therapy for newly diagnosed high-grade glioma. The first trial, a pilot study to assess the toxicity of carmustine [BCNU; 1,3-bis(2-chloroethyl)-1-nitrosourea] and hyperfractionated radiation therapy (180

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cGy three times daily to a total of 6,000 cGy), enrolled 18 patients between April and August 1987. The second trial, a phase III study of radiation therapy (6,000 cGy in 30 fractions) in combination with either BCNU or another nitrosourea derivative [PCNU; 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea] accrued 46 Mayo patients from July 1985 to April 1988. For both studies, patients were 18 years of age or older and had histologically confirmed supratentorial grade 3 or 4 astrocytoma, mixed astrocytoma-oligodendroglioma, or gliosarcoma. The performance status was categorized from 0 to 3 (Eastern Cooperative Oncology Group). None of the patients had prior chemotherapy or other coexistent malignant disease. Surgical procedures included biopsy only, partial resection, or gross total resection.

Prophylaxis against TE was implemented at the discretion of the physician in charge of the patient. An episode of TE was diagnosed clinically by the physician responsible for the care of the patient and usually was confirmed by any of the following methods: impedance plethysmography, venography, duplex ultrasonography, ventilation-perfusion lung scanning, or pulmonary angiography.

***Compilation of Data.***—Data collected prospectively for each clinical trial included age, sex, performance status, histologic features and grade of the tumor, randomization date, and survival. Data obtained retrospectively were surgical dates, duration and extent of the surgical procedure, any operation within the 3 months before randomization, duration of anesthesia, duration of hospitalization, duration of bed rest, ambulatory status, history of smoking, use of aspirin, use of glucocorticoids, type of TE prophylaxis, prior TE, and presence or absence of diabetes, obesity, hypertension, chronic lung disease, paretic arm, or paretic leg. The medical records were reviewed for the absence or presence of TE, the number of days the symptoms were present before TE was diagnosed, the type of TE documented, the diagnostic method used, the type of treatment and the related side effects, and the cause of death.

***Statistical Analysis.***—In a limited, carefully monitored group of patients, we searched for clues about possible risk factors for development of TE. The distributions of all potential prognostic factors were compared between the patients with and those without TE by using $\chi^2$ and Fisher's exact tests for nominal discrete variables, Wilcoxon tests for ordinal discrete and continuous variables, and log-rank tests for censored survival data. Survival distributions were estimated with Kaplan-Meier curves. Inasmuch as false-positive findings were highly likely because of multiple testing, $P$ values between 0.01 and 0.05 were considered "interesting" but inconclusive. With only 18 TEs noted in 64 patients, the study had little power to detect distributional differences of clinical interest.

## RESULTS

Of the 64 study patients, 18 (28%) had TE, 11 (17%) had DVT, 5 (8%) had pulmonary emboli, and 2 (3%) had superficial thrombophlebitis. DVT was diagnosed clinically with use of venography in eight patients, impedance plethysmography in two, and physical examination in one. The two patients with superficial thrombophlebitis were diagnosed by physical examination. The time from surgical intervention to diagnosis of TE ranged from 1 to 288 days (median, 66 days or 9.4 weeks).

Patients with TE had a greater frequency of paretic extremities than did those without TE—a paretic extremity was found in 15 (83%) of the TE group and in 22 patients (48%) without TE ($P<0.012$). Both patients with a history of prior TE were in the TE group ($P = 0.076$). Interestingly, all 10 patients who used aspirin preoperatively were in the non-TE group (22% versus 0%; $P = 0.05$). No information was available about aspirin dose levels, reasons for its use, or continuation of such use after operation. No major difference was noted in the use of heparin or intermittent pneumatic compression of the lower extremities in the TE versus the non-TE group. All patients with TE except the two with superficial thrombophlebitis were treated with heparin and warfarin sodium. One patient had a fatal intracerebral hemorrhage shortly after beginning warfarin therapy for pulmonary emboli. At the time of the hemorrhage, the prothrombin time was 2.6 times the control value; thus, excessive anticoagulation was suspected.

No major differences between the patients with and those without TE were found in any other variable studied, including age, duration of surgical procedure, and ambulation. Survival did not differ between the two groups; the median duration of survival was 39.4 weeks for the TE group and 46 weeks for the non-TE group.

## DISCUSSION

In the current study, we found an incidence of TE similar to that reported in the literature. In 18 of the 64 patients with high-grade astrocytoma (28%), TE developed. Numerous clinical variables are associated with an increased risk of TE, including previous history of TE, advanced age, malignant disease, immobility, congestive heart failure, obesity, use of oral contraceptives, presence of varicose veins, preoperative leg weakness, and surgical duration of more than 4 hours.[4,5] We performed univariate statistical analyses to compare the distributions of 17 variables between the TE and non-TE groups and found a higher proportion of patients with a paretic arm ($P = 0.017$), a paretic leg ($P = 0.026$), or a history of TE before diagnosis of glioma ($P = 0.076$) in the TE than in the non-TE group. Interestingly, the use of minidoses of heparin or pneumatic compression of the lower extremities was not associated with a decreased incidence of TE, al-

though a large sample size might be necessary to detect any benefit of such interventions.

In 1975, Kayser-Gatchalian and Kayser[6] reported an increased incidence of DVT in patients with brain tumors. Those investigators, who reviewed 334 autopsy reports of patients with brain tumors, found an incidence of DVT of 27.5% (92 cases); in the control group of 100 autopsies done in patients without brain tumors, the incidence was 17% ($P<0.05$). Of the 206 postsurgical patients, 56 (27.2%) had thrombosis. Of the 128 non-postsurgical patients, 36 (28.1%) had thrombosis. Of these TEs, 76 (82.6%) were found in the femoral and popliteal veins, and among these, pulmonary embolisms had occurred in 71 cases (93%). No association was noted between the histologic findings and the incidence of TE. In 1980, Valladares and Hankinson[7] reported a 29% incidence of DVT in 100 neurosurgical patients who had undergone major cranial or spinal operations. Levi and associates[8] retrospectively reviewed the incidence of TE in 1,703 patients who had undergone craniotomy for meningioma, glioma, or brain metastatic lesions. Within the first 4 weeks after the craniotomy, 27 patients (1.59%) had clinical evidence of DVT or pulmonary embolism. The tumor-specific rates of TE were 3.09% for meningioma, 0.97% for glioma, and 1.03% for brain metastatic lesions. The surgical time was significantly longer in patients with meningioma than in those with other lesions. In 1983, Ruff and Posner[3] reported an increased incidence of DVT in patients with glioma. In that retrospective study, 37% of the patients who did not receive prophylaxis had clinical evidence of DVT that was confirmed by venography. In a second group of patients who received prophylaxis with intermittent pneumatic compression of both lower extremities, those investigators noted an incidence of DVT of 10% ($P<0.05$).

Our study supports the experience of other groups of investigators in the use of anticoagulants for treating TE in patients with brain tumors. We observed bleeding complications in 1 of 5 patients with pulmonary embolism and in none of 11 patients with DVT; all these patients received heparin followed by warfarin sodium. The patient who died had a prothrombin time that was 2.6 times the control value, and excessive anticoagulation was suspected. Our two patients with superficial thrombophlebitis received no anticoagulant therapy. Ruff and Posner[3] reported that anticoagulation decreased the risk of pulmonary embolism without increasing the risk of intracranial bleeding. Of their 109 patients with phlebitis, 103 were treated intravenously with heparin followed by warfarin sodium for 6 to 14 weeks; 6 patients refused treatment. Only one patient who received anticoagulants had a nonfatal pulmonary embolism, whereas three of six patients who refused treatment died of pulmonary embolism ($P<0.05$). In that same study,[3] patients with paretic extremities had an increased incidence of TE. In 1987, Choucair and colleagues[9] reported the experience of the University of California, San Francisco, in the use of anticoagulant therapy in patients with brain tumors. In that retrospective study of 915 patients, TE developed in 36 (4%) more than 30 days after operation. Of these 36 patients, 27 (75%) had pulmonary embolism; 10 of these patients died suddenly, and 17 survived long enough to receive anticoagulant therapy with intravenously administered heparin followed by 3 to 6 months of either subcutaneously administered heparin or orally administered warfarin sodium. None of the treated patients experienced intracranial bleeding. Collectively, these reports suggest that careful control of the anticoagulation status can result in a decreased risk of TE.

Our retrospective review found that no patient who took aspirin before operation for high-grade glioma subsequently had TE. The use of aspirin in the prevention of arterial thrombosis is well recognized;[10] its use in the prevention of venous thrombosis has not been established. Clagett and Reisch[11] performed a meta-analysis of randomized clinical trials that evaluated methods of preventing DVT in general surgical patients (patients who underwent orthopedic or neurosurgical procedures were excluded from analysis). All the studies had a control arm with no treatment. In their evaluation of use of aspirin in 762 patients from five randomized trials, aspirin did not decrease the incidence of TE in comparison with a placebo ($P = 0.33$).

The trial of the Medical Research Council of Britain is the most frequently cited negative study.[12] This prospective, randomized, placebo-controlled trial of the effect of aspirin in the prevention of DVT included 150 patients in the placebo group and 153 patients in the aspirin group. (Orthopedic and neurosurgical procedures were excluded from analysis.) DVT was diagnosed by $^{123}$I-fibrinogen uptake. DVT developed in 22% of the patients in the placebo group and 27% of the patients in the aspirin group ($P>0.3$). In a prospective, double-blind, placebo-controlled study, Harris and coworkers[13] assessed the use of aspirin for preventing deep venous TE in patients who underwent total hip replacement. TE developed in 11 of 44 patients who received aspirin in comparison with 23 of 51 who received placebo. The difference was statistically significant only in male patients. The results of other investigations, however, have been negative.[14]

## CONCLUSION

In our review of the occurrence of clinically detectable TE in Mayo Clinic patients with high-grade glioma in two prospective studies in which radiation therapy and chemotherapy were used, we found an incidence of TE of 28%. The presence of a paretic extremity and a history of TE before

glioma was diagnosed were more common in patients with TE than in those without TE. The preoperative use of aspirin seemed to decrease the risk of TE, although we had no information about the use of aspirin postoperatively. The presence of TE did not seem to decrease the duration of survival. One fatal complication was associated with the use of anticoagulants in this group of 64 patients with high-grade glioma.

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