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Full Length Article

Management of venous thromboembolism in patients with glioma

Mosaad Al Megren [a], Carine De Wit [c], Mohammad Al Qahtani [b], Grégoire Le Gal [c], Marc Carrier [c,*]

[a] College of Medicine, Al Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia
[b] Department of Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia
[c] Department of Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada

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ABSTRACT

Background: Venous thromboembolism (VTE) is a common complication among patients with glioma. However, data on the safety of therapeutic doses of anticoagulation is scarce in this patient population.
Objectives: The purpose of this study is to evaluate the risk of intracranial hemorrhage (ICH) in glioma patients receiving therapeutic anticoagulation for VTE treatment.
Patients and methods: We conducted a case-control study including glioma patients with and without acute VTE from Jan 2010 to March 2015. Controls were matched based on age, gender and tumor grade.
Result: 569 patients with glioma were identified, 76 (13.3%) developed acute VTE. Of the 70 patients treated with full dose anticoagulant therapy, 14 (20%) patients had a major bleeding including 11 (15.7%) ICH. The odds ratio for ICH in patients with glioma and VTE who were treated with anticoagulation compared to the control group was 7.5 (95% CI, 1.6–34.9) $p = 0.01$. Overall survival was similar for VTE and control group (36 vs. 42 months, $p = 0.93$).
Conclusion: Therapeutic anticoagulation is associated with a 7-fold increase risk of ICH in glioma patients. Data emerging from this study support the need for high quality studies to evaluate the risk of ICH in patients with glioma and VTE.

1. Introduction

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a frequent complication in patients with cancer; the risk varies among different types of cancers. Patients with gliomas are particularly at high risk for VTE and its complications [1]. Symptomatic VTE can develop in up to 30% of patients with glioma [2,3]. Early treatment of VTE with anticoagulant therapy is essential to minimize the risk of recurrent events and avoid its associated long-term complications.

The possibility of potentially inducing intracranial hemorrhage (ICH) after the initiation of therapeutic doses of anticoagulants in patients with brain tumors remains an important concern among clinicians. Intracranial hemorrhage can be a major complication of anticoagulation in this patient population, with a reported mortality rate as high as 45% [4]. Therefore, clinicians can be reluctant in initiating anticoagulation, and patients with brain tumors and VTE are often treated with the placement of an inferior vena cava (IVC) filter rather than therapeutic anticoagulation [5]. However, the use of IVC filters in these patients has been associated with a high risk of complication (up to 62%) after filter placement [5]. The majority of IVC filter complications in this particular study were related to thrombotic events, suggesting that these devices may be ineffective for the management of VTE in this patient population. Moreover, a recent matched controlled study has suggested that although ICH is a frequent complication in patients with brain metastases, therapeutic anticoagulation did not seem to further increase the risk of ICH [6].

Thus, clinical practice guidelines currently suggest initiation of therapeutic anticoagulation in patients with metastatic brain disease or primary intra-cranial tumors without active bleeding [7]. Nonetheless, the risk of ICH associated with therapeutic anticoagulation in glioma patients remains unclear and warrants further evaluation. In order to address this knowledge gap, we sought to determine the risk of ICH and its associated risk factors in glioma patients with acute VTE who are treated with anticoagulation.

2. Methods

We conducted a retrospective case control study of consecutive glioma patients with VTE including DVT and PE, and cerebral vein thrombosis (CVT) seen at The Ottawa Hospital (TOH) between January 2010 and March 2015. Each case was matched with one glioma patient without VTE (control). Controls were matched based on age (±10 years),

* Corresponding author at: The Ottawa Hospital General Campus, 501, Smyth Road, Box 201A, Ottawa, ON K1H 8L6, Canada.
E-mail address: mcarrier@toh.ca (M. Carrier).

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gender and tumor grade (WHO classification). The presence of symptomatic VTE had to be confirmed by diagnostic imaging.

Data were collected by reviewing the electronic medical record for each identified patient. The following data were collected: age, gender, type of VTE, anticoagulation, the rate of bleeding complications, tumor size, tumor grade, type of surgery, leg paresis, use of chemotherapy, and IVC filter, and the overall outcome. Follow-up data was extracted from the time of glioma diagnosis to the last encounter date, death, or end of study (August 2015). The primary outcome of the study was ICH defined as any bleeding into the cranial vault over the follow-up period. Secondary outcomes were overall survival and major bleeding. Major bleeding was defined according to International Society on Thrombosis and Haemostasis (ISTH). Cerebral vein thrombosis was defined as thrombosis of the cerebral venous sinuses with or without cortical or deep veins involvement. Pulmonary embolism was defined as an intraluminal filling defect in the pulmonary arteries up to the segmental arteries on the computed tomography pulmonary angiogram (CTPA) or high probability ventilation perfusion scan (V/Q). Proximal lower limb deep vein thrombosis was defined as lack of compressibility or absence of Doppler flow, or direct visualization if thrombus involving popliteal veins and above, while distal deep vein thrombosis was defined as thrombosis limited to infrapopliteal veins.

2.1. Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23.0. The Fisher's exact test/Chi-Square Test was used for comparing the categorical variables and the primary outcome of the study (ICH) in patients with or without VTE. The analysis of variance (ANOVA) was used for the evaluation of continuous variables. To evaluate overall survival the method of Kaplan and Meier was used based on the date of initial assessment for cases and controls, and the log-rank test was employed to characterize survival difference based on considered variables included in this study. The Cox proportional hazard method was applied for univariate analysis as well as hazard ratios. A $p < 0.05$ was the criterion for significance.

3. Results

A total of 569 consecutive glioma patients were identified (Fig. 1). Seventy-six (13.3%) of these patients were diagnosed with acute VTE and formed the group of cases. Seventy-six patients without VTE with matched age, gender, and tumor grade were selected as the control group. The baseline characteristics of all patients are depicted in Table 1. The mean age of the patients was 59 (standard deviation SD 13.95) years. The group consisted of one hundred and ten (72%) male patients and forty-two (28%) female patients. There were no significant differences between glioma patients who developed VTE and those who did not (Table 1). Of the VTE group ($n = 76$), 40 (52%) patients experienced DVT (7 distal and 33 proximal DVT), 16 (21%) PE, 19 (25%) both and 1 patient developed CVT. Treatment of VTE included IVC filter, anticoagulation or both modalities of treatment. Among cases, three VTE occurred prior to surgery. Overall, 14, 29 and 29 patients had their VTE < 14 days, 2–12 weeks, >22 weeks following neurosurgery, respectively. One patient did not undergo surgery.

Seventy (92%) patients were treated with therapeutic anticoagulation; of them, 56 (74%) patients were treated with therapeutic anticoagulation alone, whereas 14 (18%) patients received therapeutic anticoagulation in addition to an IVC filter insertion. Of the seventy patients who were treated with therapeutic anticoagulation, 62 (88.5%) patients received therapeutic weight-adjusted low molecular weight heparin (LMWH), 6 (8.5%) patients with unfractionated heparin

Table 1
Characteristics of patients with and without venous thromboembolism.

Factor	Patients without VTE $N = 76$	VTE $N = 76$	p value
Mean age in years ± SD	59.1 ± 14.2	59.6 ± 13.7	
Gender			
Female	21 (27.6)	21 (27.6)	
Male	55 (72.4)	55 (72.4)	
Tumor grade			
Low	2 (2.6)	2 (2.6)	
High	74 (97.4)	74 (97.4)	
Tumor size			
<5 cm	48 (66.7)	41 (56.2)	0.194
>5 cm	24 (33.3)	32 (43.8)	
Neurosurgery			
No	0	1 (1.3)	1.000
Yes	76 (100)	75 (98.7)	
Type of surgery			
Biopsy	16 (24.6)	22 (36.7)	0.143
Resection	49 (75.4)	38 (63.3)	
IVC filter			
No	76 (100)	59 (77.6)	<0.001
Yes	0	17 (22.4)	
Leg paresis			
No	48 (63.2)	47 (61.8)	0.867
Yes	28 (36.8)	29 (38.2)	
Chemotherapy			
No	23 (30.3)	14 (18.4)	0.089
Yes	53 (69.7)0	62 (81.6)	

Data represented as n (%); SD, Standard deviation.

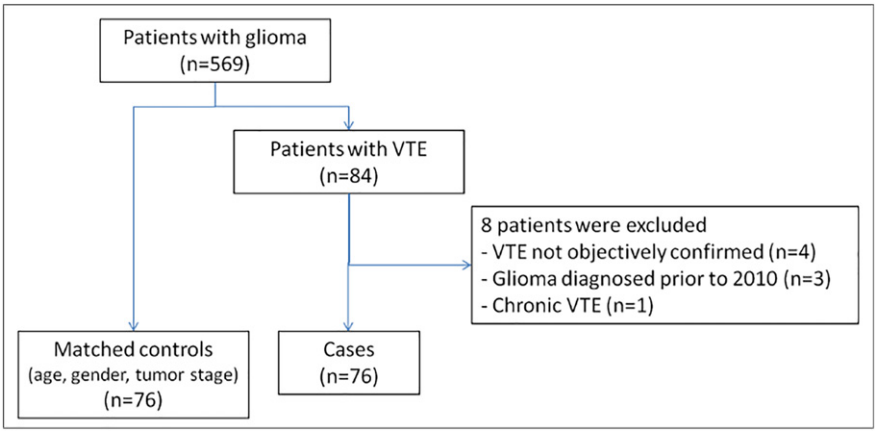

Fig. 1. Study flow chart.