Management of venous thromboembolism in patients with glioma

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[Title: Management of venous thromboembolism in patients with glioma]

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Highlights

- Management of venous thromboembolism in patients with glioblastoma is challenging
- The risk of intracranial bleeding is increased 7-fold on anticoagulant therapy
- No significant predictor of the risk of bleeding could be identified

Keywords

Glioma, venous thromboembolism, venous thrombosis, hemorrhage, neoplasm
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.
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.

**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), 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.

**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 were 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.

**Results**
A total of 569 consecutive glioma patients were identified (Figure 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 (UFH), one patient with fondaparinux and unknown type of anticoagulation in one patient. Median duration of anticoagulation was 27 days. Among patients who were not treated with therapeutic anticoagulation, three patients had an IVC filter insertion concurrently with prophylactic anticoagulation, two patients were
managed with prophylactic anticoagulation only, and one patient with distal DVT was
managed with neither prophylaxis nor IVC filter. A total of 69 (91%) controls that
underwent neurosurgery received thromboprophylaxis during the post-operative period.

The median follow-up time for all patients (n=152) was 11 months (range 1-66 months).
Thirty nine patients (25.7%) died during follow up. Among the glioma patients with VTE
who were treated with therapeutic anticoagulation (n=70), a total of 14 patients (20%,
95% CI 10.8-30) developed a major bleeding episode, including 11 ICH (15.7%, 95% CI
7.5-24.6), as compared to 3 patients (2 ICH) in the patients without VTE. Median time
between initiation of anticoagulation and bleeding was 27 days. Platelet count at the time
of the bleeding episode ranged between 113 and 338 G/L. The Odds Ratio of major
bleeding episode and ICH in patients receiving therapeutic anticoagulation were 6.6 (95%
CI: 1.8-24.0; p=0.004) and 7.5 (95% CI 1.6-34.9, p= 0.01), respectively (Table 2). One of
the major bleeding events in the VTE group was fatal. Univariate risk regression analyses
performed to identify potential variables predictive of ICH are reported in Table 3.
Tumor size, type of surgery, chemotherapy, leg paresis, and time between neurosurgery
and initiation of anticoagulation were not associated with an increased risk of ICH. There
were no recurrent VTE.

A Kaplan-Meier survival analysis showed median survival was similar between glioma
patients with and without VTE (36 vs. 42 months, p=0.93). Similarly, there was no
significant difference in median survival in patients who had ICH and those who did not
(42 vs. 52 months, p= 0.21).
Discussion

The risk of ICH is high among glioma patients receiving therapeutic doses of anticoagulation. This provides important insight about the risk of ICH and will help clinicians to establish the risk benefit ratio in this patient population.

Our findings are consistent with previously published literature on VTE management in glioma patients (2,3). In our study, the incidence of ICH was 15.7% (95% CI 7.5 – 24.6) in those treated with therapeutic anticoagulation. The reported incidence of ICH in this population varies across previous studies but is similar to the incidence reported in our analysis. In a retrospective study investigating the incidence of ICH in patients with glioma and VTE, 3 (12%) out of 25 patients who were treated with anticoagulation developed ICH (8). In another recent study, the incidence of ICH in patients who received anticoagulation was 16% (9).

Our study reported a 7-fold higher risk of ICH among glioma patients receiving therapeutic anticoagulation compared to those that did not. A recent meta-analysis including five studies that reported outcomes of glioma patients has similarly shown that therapeutic anticoagulation increases the risk of ICH by 3.8 fold (10).

Interestingly, our results indicate that the survival rate in patients who developed VTE was similar to those who did not (p = 0.93). This could be explained by a relative short survival rate in patients with high grade glioma in general. Similarly, the survival rate of
glioma patients with VTE who developed ICH was similar to those who did not (p = 0.21). These findings are again consistent with previous literature. Khoury and colleagues did not find any survival differences between patients who developed ICH and those who did not (12.2 vs 10 months, p = 0.4) (9). A study reporting the impact of VTE on survival in patients with high grade glioma also failed to demonstrate any differences in survival between patients with and without VTE (11).

There was no recurrent VTE reported in our study. In contrast, a retrospective study of 145 patients with glioma and VTE, 39 patients (27%) developed recurrent VTE, despite 60% of them being treated with anticoagulation, however more than half of patients with recurrent VTE were managed concurrently with IVC filter and most patients were not on anticoagulation at the time of recurrence (12). Another study reported on 42 patients with brain tumors who were managed with IVC filter only: 62% developed complications related to the filter insertion (5). In another retrospective study of 51 patients with brain metastasis, 4 out of 10 patients who were managed with IVC filter alone had a recurrent VTE (13). The high rate of therapeutically anticoagulated patients in our study (92%) and low rate of filter placement alone (4%) could explain the absence of VTE recurrence and suggests that anticoagulation might be effective in preventing recurrent events in this patient population. For primary brain tumors, the American Society of Clinical Oncology recommends anticoagulation with careful monitoring given the risk of bleeding, and does not support the routine use of IVC filter (6).
Our study is limited by its retrospective nature and the involvement of patients seen at single center. No *a priori* sample size calculation was performed. Furthermore, the total number of ICH is relatively small and the differences in variables in the development of ICH could maybe not be appreciated given the limited sample size. Our limited sample size also prevented us for performing further subgroup analyses. In particular, we were unable to identify useful predictors of the risk of bleeding in glioma patients with VTE who were treated with anticoagulant therapy. For example, it is debatable if these results are applicable to all grades of GBM, given that the vast majority of included patients had high grade disease. Finally, additional risk factors (e.g. creatinine clearance) could not be extracted and analyzed. Given these limitations, our study should be considered as hypothesis-generating only.

In summary, VTE is common in patients with glioma. Anticoagulation increases the risk of ICH in patients who developed VTE. However, the overall survival of patients who developed ICH was similar to those who did not. Given the high rate of complications and recurrent VTE associated with IVC filter alone, anticoagulation in appropriately selected patients seems reasonable practice with careful monitoring for bleeding. Additional prospective studies are urgently needed to clarify the role and risk of anticoagulation in patients with glioma.
Addendum

Author Contributions

All authors have fulfilled the conditions required for authorship.

MAM – designed and performed research; analyzed and interpreted data; wrote manuscript

CDW – collected data; provided vital reviews to the manuscript.

MAQ- interpreted data; provided vital reviews to the manuscript.

GLG – interpreted data; provided vital reviews to the manuscript.

MC – designed research; interpreted data; provided vital reviews to the manuscript.

Conflicts of Interest

No relevant conflict of interest to disclose

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GLG is the recipient of an Early Researcher Award from the Province of Ontario, a Heart and Stroke Foundation of Ontario Clinician Scientist CP has heart Cardiovascular Award, and holds a Chair on Diagnosis of Venous Thromboembolism from the Department of Medicine, University of Ottawa.
References


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Figure 1. Study flow chart

Patients with glioma (n=569)

Patients with VTE (n=84)

Matched controls (age, gender, tumor stage) (n=76)

Cases (n=76)

8 patients were excluded
- VTE not objectively confirmed (n=4)
- Glioma diagnosed prior to 2010 (n=3)
- Chronic VTE (n=1)
Table 1. Characteristics of patients with and without venous thromboembolism

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

Data represented as n (%); SD, Standard deviation
Table 2. Overall risk of anticoagulation therapy

<table>
<thead>
<tr>
<th>Factor</th>
<th>ICH</th>
<th>ICH</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Anticoagulation status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No anticoagulation</td>
<td>80 (97.5)</td>
<td>2 (2.4)</td>
<td>Ref</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>59 (84.3)</td>
<td>11 (15.7)</td>
<td>7.5 (1.6-34.9)</td>
</tr>
</tbody>
</table>

Data represented as n (%), CI, confidence interval; Ref, Reference
Table 3. Univariate analysis for the development of intracranial hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.96 (0.93-1.0)</td>
<td>0.055</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>2.22 (0.47-10.47)</td>
<td>0.313</td>
</tr>
<tr>
<td>Tumor size (&gt;5cm)</td>
<td>1.66 (0.50-5.42)</td>
<td>0.402</td>
</tr>
<tr>
<td>Type of surgery (Resection)</td>
<td>1.57 (0.31-7.95)</td>
<td>0.583</td>
</tr>
<tr>
<td>Leg paresis</td>
<td>1.47 (0.47-4.64)</td>
<td>0.502</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>4.99 (0.63-39.31)</td>
<td>0.127</td>
</tr>
<tr>
<td>Time between neurosurgery and start of anticoagulation</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>&lt;14 days</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>2 – 12 Weeks</td>
<td>0.26 (0.01-4.74)</td>
<td>0.368</td>
</tr>
<tr>
<td>&gt; 12 weeks</td>
<td>2.08 (0.21-20.09)</td>
<td>0.524</td>
</tr>
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CI, Confidence interval