Length of thromboprophylaxis in patients operated on for a high-grade glioma: a retrospective study

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Length of Thromboprophylaxis in Patients Operated on for a High-Grade Glioma: A Retrospective Study.

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■ OBJECTIVE: **High-grade gliomas are associated with venous thromboembolism (VTE). This retrospective study with a parallel cohort design investigated influence of continuing prophylactic anticoagulation after discharge on rate of VTE and intracranial hemorrhage (ICH) in patients operated on for high-grade glioma.**

■ METHODS: **Consecutive adult patients who underwent subtotal or gross total resection for high-grade glioma at a single institution were included. Multivariable logistic regression analysis was used to investigate the association between duration of thromboprophylaxis (dalteparin administered 21 days vs. 0–7 days) and occurrence of VTE and ICH within 21 or 90 days after surgery, corrected for known risk factors.**

■ RESULTS: **Of 301 included patients, 166 received short-term thromboprophylaxis, and 135 received prolonged thromboprophylaxis. In multivariable analysis, prolonged thromboprophylaxis was not significantly associated with occurrence of VTE within 21 days (3.0% vs. 1.2%; $P = 0.24$) or 90 days (8.9% vs. 4.8%; $P = 0.09$) after surgery; however, prolonged prophylaxis was associated with occurrence of ICH (5.9% vs. 0.6%; $P = 0.03$). Additionally, immobility ($P = 0.03$) and high body mass index ($P = 0.02$) were associated with occurrence of VTE.**

■ CONCLUSIONS: **Prophylactic anticoagulation for 21 days postoperatively was not associated with a decreased rate of VTE compared with thromboprophylaxis until discharge. ICH was more common with prolonged thromboprophylaxis. These results provide insufficient evidence to extend duration of prophylaxis beyond hospitalization. Large-scale randomized prospective studies are needed to clarify safety, efficacy, and optimal timing of postoperative thromboprophylaxis in patients with high-grade glioma.**

INTRODUCTION

Patients with cancer are at increased risk for venous thromboembolism (VTE). This risk is especially high in patients with brain tumors.[1] Among the different brain tumors, high-grade gliomas (HGGs) seem to be particularly associated with risk for developing a VTE,[2-4] with reported incidences of symptomatic VTE up to 37% throughout the course of the disease, depending on the follow-up time and prophylactic treatment given.[4-18] Although it is controversial whether VTE reduces survival in patients with HGGs,[2,4,6-8,14,19] VTE reduces their quality of life and remains one of the main reasons for readmission within 30 days after surgery.[20] Besides neurosurgery, many other patient-, tumor-, and treatment-related risk factors for the development of VTE have been identified in patients with HGGs, including old age,[3,5,8,21] male sex,[15] obesity,[15] history of VTE,[6,15] blood group A or AB compared with O,[5] elevated factor VIII,[19] low Karnofsky Performance Scale score,[3,15,21] paresis,[2-4,17,18] seizures,[6] glioblastoma histology,[4,8] large tumor size,[5] supratentorial location,[2] intraluminal thrombosis in

Key words
- High-grade glioma
- Intracranial hemorrhage
- Low-molecular-weight heparin
- Thromboprophylaxis
- Venous thromboembolism

Abbreviations and Acronyms
BMI: Body mass index
CI: Confidence interval
HGG: High-grade glioma
ICH: Intracranial hemorrhage
LMWH: Low-molecular-weight heparin
OR: Odds ratio
VTE: Venous thromboembolism

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Table 1. Baseline Characteristics Compared by Duration of Postoperative Thromboprophylaxis

Patient Characteristic	0–7 Days LWMH (n = 166)	21 Days LMWH (n = 135)	P Value
Age, years, mean ± SD	56.5 ± 13.5	59.2 ± 12.7	0.09
Female sex, number (%)	70 (42.2)	55 (40.7)	0.90
BMI, kg/m^2, mean ± SD	26.0 ± 4.8	26.1 ± 4.2	0.89
Histology, number (%)			
AA	9 (5.4)	10 (7.4)	0.11
AOA	4 (2.4)	11 (8.1)	
AO	2 (1.2)	1 (0.7)	
GB	151 (91.0)	113 (83.7)	
WHO grade IV, number (%)	151 (91.0)	113 (83.7)	0.08
IDH1 mutation, number (%)	8 (7.1)	12 (13.6)	0.19
LOS, days, median (IQR)	8 (7–10)	7 (6–9)	0.006
Subtotal resection, number (%)	68 (41.0)	99 (73.3)	<0.001
Awake surgery, number (%)	5 (3.1)	55 (42.3)	<0.001
Operative time, minutes, median (IQR)	190 (150–240)	165 (120–210)	0.001
Dexamethasone, number (%)	148 (89.2)	132 (97.8)	0.007
Postoperative KPS score ≥70, number (%)	74 (88.1)	97 (82.9)	0.41
Postoperative immobility, number (%)	14 (8.4)	8 (5.9)	0.54
History of VTE, number (%)	0 (0)	3 (2.2)	0.18
History of malignancy, number (%)	20 (12.2)	18 (13.3)	0.91
Radiotherapy, number (%)	149 (91.4)	124 (91.9)	1.00
Chemotherapy, number (%)	134 (82.2)	100 (74.1)	0.12

LMWH, low-molecular-weight heparin; BMI, body mass index; AA, anaplastic astrocytoma; AOA, anaplastic oligoastrocytoma; AO, anaplastic oligodendroglioma; GB, glioblastoma; WHO, World Health Organization; LOS, length of stay; IQR, interquartile range; KPS, Karnofsky performance scale; VTE, venous thromboembolism.

glioma vessels,[22] craniotomy,[3,7,8,12] initial biopsy before resection,[19] residual tumor tissue after surgery,[7] increased postoperative stay in the intensive care unit[6] or in the hospital,[21] number of hospital admissions,[21] steroid usage,[15] chemotherapy,[18,23] and anti–vascular endothelial growth factor therapy.[21]

Most guidelines recommend use of low-molecular-weight heparins (LMWHs), often in combination with compression stocking and/or intermittent pneumatic compression, in patients operated on for a brain tumor to reduce the risk of VTE; however, proper timing of prophylaxis is controversial and varies from administration throughout hospitalization,[24] up to 7–10 days after surgery,[25-27] until the patient is mobile,[28] to timing based on the patient's risk profile or the surgeon's preference.[29,30] A lack of scientific evidence is primarily the cause of this variation in recommendations, and the risk of intracranial hemorrhage (ICH) make many neurosurgeons lean toward a more conservative thromboprophylactic strategy.[31] However, a recent study demonstrated that the risk of VTE remains considerably high after discharge, especially for pulmonary embolism, whereas ICH occurred predominantly during hospitalization.[32] This suggests a potential role for continuing LMWH administration beyond discharge.

In our institution, the duration of postoperative thromboprophylaxis has been prolonged up to 21 days after surgery for an extended period of time. This provides the opportunity to assess the effectiveness of this policy and make a direct comparison with the conventional strategy of prophylactic anticoagulation administered until discharge from the hospital. In this retrospective cohort study, we assessed whether prolonged thromboprophylaxis decreases the rate of postoperative VTE compared with short-term prophylaxis and investigated the association of prolonged thromboprophylaxis with the occurrence of ICH.

MATERIALS AND METHODS

Subjects

All adult patients who were operated on for HGG (World Health Organization grade III or IV) at University Medical Center Utrecht, The Netherlands, between January 1, 2007, and June 30, 2013, were eligible for this study. Exclusion criteria were age <18 years at time of surgery and previous craniotomy. The hospital's medical ethics committee stated that the national laws of the Medical Research Involving Human Subjects Act did not apply to this study.

Outcomes

The primary outcomes were the occurrence of VTE (within 21 days and 90 days) and postoperative ICH. VTE was defined as clinical

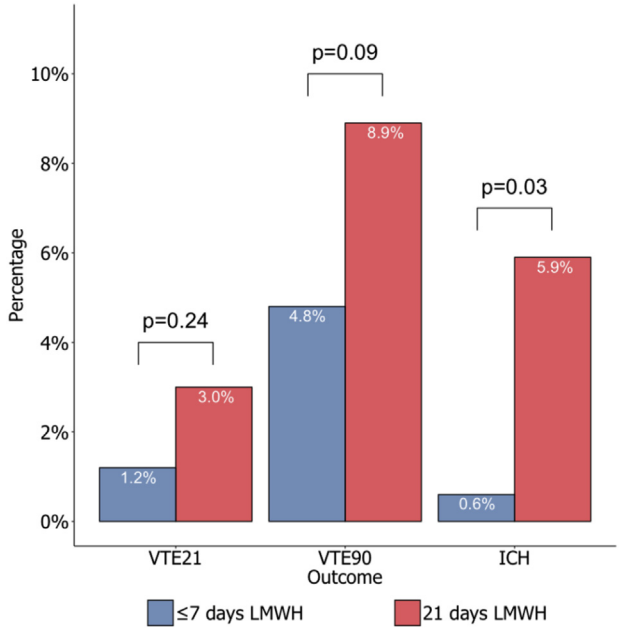

Figure 1. Incidence of venous thromboembolism and intracranial hemorrhage compared by duration of postoperative thromboprophylaxis. VTE21, venous thromboembolism within 21 days after surgery; VTE90, venous thromboembolism within 90 days after surgery; ICH, intracranial hemorrhage; LMWH, low-molecular-weight heparin.

symptoms of deep venous thrombosis or pulmonary embolism confirmed by Doppler ultrasonography or computed tomography angiography, respectively. ICH was defined as a postoperative hemorrhage requiring surgical evacuation. Because all ICHs occurred in the immediate postoperative period, no distinction was made based on the timing of follow-up.

Thromboprophylaxis and Other Covariates

Subcutaneous dalteparin (5000 IU/day) was administered according to the surgeon's preference. In 2010, 2 neurosurgeons started continuing thromboprophylaxis up to 21 days after surgery. The other surgeons administered thromboprophylaxis until discharge from the hospital (0–7 days). This difference in policy was driven by the physician's preference rather than by patient characteristics. Other variables collected from the electronic health records were sex, age, body mass index (BMI), prior history of malignancy or VTE, steroid usage, tumor histology, length of hospitalization, extent of resection reported by the neurosurgeon (subtotal or gross total resection), intraoperative functional mapping, operative time, postoperative Karnofsky performance scale score, postoperative immobility, and adjuvant chemotherapy and radiotherapy. Postoperative immobility was defined as weakness in a lower limb and/or walking difficulties.

Analysis

Univariable analysis was performed to explore the relationship between the independent variables and the occurrence of VTE and ICH. Chemotherapy and radiotherapy were not included in the analysis of VTE within 21 days because these adjuvant therapies were generally started 6 weeks after surgery. Similarly, Karnofsky performance scale score, immobility, and length of stay were not included in the analysis of ICH because these variables were assessed after the occurrence of all ICH events. We considered these variables to be a result of, rather than a cause of, the occurrence of ICH. Subsequent multivariable analysis was aimed at determining the independent contribution of each variable to the risk of postoperative VTE or ICH.

χ^2 test and independent sample t test were used in the univariable analysis for categorical and continuous data, respectively. Mann-Whitney U test was used for nonparametric continuous data. Variables associated with VTE in the univariable analysis were included in the multivariable logistic regression analysis, with a liberal threshold ($P < 0.20$) to include all determinants with potential value. Firth regression analysis was performed if 1 of the cells in the multivariable analysis contained zero events. Given our interest in the duration of LMWH thromboprophylaxis, this variable was included in the multivariable analysis automatically. A probability level <0.05 was considered statistically significant. The β coefficients of the continuous variables in the final multivariable models were multiplied to represent the odds ratios (ORs) and confidence intervals (CIs) of meaningful and interpretable units for age (per 10 years increase) and BMI (per 5 kg/m^2 increase). IBM SPSS Version 24 (IBM Corp., Armonk, New York, USA) was used to perform all statistical analyses.

RESULTS

Between 2007 and 2013, 313 patients underwent craniotomy for HGG. Of 313 patients, 12 were excluded because of a previous craniotomy ($n = 10$) or age <18 years at time of surgery ($n = 2$). Therefore, 301 patients were included in the analysis; 166 patients received short-term prophylaxis, and 135 received prolonged prophylaxis. Baseline characteristics compared by thromboprophylactic regimen are shown in Table 1. In the short-term prophylaxis group, 2 (1.2%) patients developed a VTE within 21 days, and 8 (4.8%) patients developed a VTE within 90 days compared with 4 (3.0%) patients and 12 (8.9%) patients, respectively, in the prolonged prophylaxis group (Figure 1). In the short-term prophylaxis group, 1 (0.6%) patient developed an ICH that required surgical evacuation compared with 8 (5.9%) patients in the prolonged prophylaxis group. All ICHs occurred within 10 days after surgery.

In the univariable analysis for occurrence of VTE, prolonged compared with short-term prophylaxis was not significantly associated with rate of VTE within 21 days ($P = 0.50$) (Table 2) or 90 days ($P = 0.24$) (Table 3). No other risk factors were identified for VTE within 21 days. Patients who developed a VTE within 90 days had a significantly higher BMI compared with patients who did not (28.1 ± 5.8 kg/m^2 vs. 25.9 ± 4.4 kg/m^2 [± SD], $P = 0.04$).

In the multivariable analysis including LMWH duration and all variables with a P value <0.20, prolonged prophylaxis was not significantly associated with rate of VTE within 21 days (OR = 2.86; 95% CI, 0.53–21.45; $P = 0.24$) or 90 days (OR = 2.19; 95% CI, 0.88–5.75; $P = 0.09$) after surgery. Additionally, immobility was associated with VTE within 21 days (OR = 7.75; 95% CI, 1.01–43.97; $P = 0.02$) and 90 days after surgery (OR = 4.15; 95% CI, 1.15–13.03; $P = 0.03$). High BMI was associated with VTE

Table 2. Univariable and Multivariable Analysis for Outcome of Venous Thromboembolism Within 21 Days

Univariable Analysis

Patient Characteristic	Total (n = 301)	No VTE ≤21 Days (n = 295)	VTE ≤21 Days (n = 6)	P Value
Age, years, mean ± SD	57.7 ± 13.2	57.8 ± 13.2	56.8 ± 11.1	0.86
Female sex, number (%)	125 (41.5)	121 (41.0)	4 (66.7)	0.40
BMI, kg/m^2, mean ± SD	26.0 ± 4.5	26.0 ± 4.5	25.5 ± 3.5	0.77
Histology, number (%)				
AA	19 (6.3)	19 (6.4)	0 (0.0)	0.84
AOA	15 (5.0)	15 (5.1)	0 (0.0)	
AO	3 (1.0)	3 (1.0)	0 (0.0)	
GB	264 (87.7)	258 (87.5)	6 (100.0)	
WHO grade IV, number (%)	264 (87.7)	258 (87.5)	6 (100.0)	0.77
IDH1 mutation, number (%)	20 (10.0)	20 (10.1)	0 (0.0)	1.00
LOS, days, median (IQR)	7 (6–10)	7 (6–10)	13 (7–19)	0.37
Subtotal resection, number (%)	167 (55.5)	164 (55.6)	3 (50.0)	1.00
Awake surgery, number (%)	60 (20.8)	59 (20.8)	1 (16.7)	1.00
Operative time, minutes, median (IQR)	180 (130–240)	180 (130–240)	190 (180–230)	0.50
21 days LMWH, number (%)	135 (44.9)	131 (44.4)	4 (66.7)	0.50
Dexamethasone, number (%)	280 (93.0)	275 (93.2)	5 (83.3)	0.90
Postoperative KPS score ≥70, number (%)	171 (85.1)	167 (85.2)	4 (80.0)	1.00
Postoperative immobility, number (%)	22 (7.3)	20 (6.8)	2 (33.3)	0.09
History of VTE, number (%)	3 (1.0)	3 (1.0)	0 (0.0)	1.00
History of malignancy, number (%)	38 (12.7)	37 (12.6)	1 (16.7)	1.00

Multivariable Analysis

Predictor	OR	95% CI	P Value
Postoperative immobility	7.75	1.01–43.97	0.02
21 days LMWH	2.86	0.53–21.45	0.24

VTE, venous thromboembolism; BMI, body mass index; AA, anaplastic astrocytoma; AOA, anaplastic oligoastrocytoma; AO, anaplastic oligodendroglioma; GB, glioblastoma; WHO, World Health Organization; LOS, length of stay; IQR, interquartile range; LMWH, low-molecular-weight heparin; KPS, Karnofsky performance scale; OR, odds ratio; CI, confidence interval.

within 90 days after surgery (OR = 1.66 per 5 kg/m^2 increase; 95% CI, 1.08–1.83; P = 0.02). In the univariable analysis for ICH, prolonged prophylaxis was significantly associated with the occurrence of ICH (P = 0.02) (Table 4). In the multivariable analysis, prolonged prophylaxis was also associated with the occurrence of ICH (OR = 9.67; 95% CI, 1.73–180.95; P = 0.03). No other risk factors for ICH were identified.

DISCUSSION

Postoperative LMWH administration for 21 days was not significantly associated with a lower rate of VTE compared with thromboprophylaxis until discharge (0–7 days). However, prolonged prophylaxis was found to be associated with the occurrence of ICH. Immobility and high BMI were identified as independent predictors of postoperative VTE.

Two case series,[9,10] 1 retrospective cohort study,[6] and 1 randomized controlled trial[11] evaluated the effect of prolonged thromboprophylaxis on VTE rate in patients with HGGs. In the case series by S. L. Perry et al.[10] and randomized controlled trial by J. R. Perry et al.,[11] thromboprophylaxis was initiated within the first 4 weeks after surgery and continued up to 12 months. The randomized controlled trial closed early because of expiration of study medication and was effectively underpowered to assess the safety and effectiveness of long-term thromboprophylaxis. Additionally, the trial did not directly compare short-term versus long-term prophylaxis because the control group received placebo instead of short-term prophylaxis. Robins

Table 3. Univariable and Multivariable Analysis for Outcome of Venous Thromboembolism Within 90 Days

Univariable Analysis

Patient Characteristic	Total (n = 301)	No VTE ≤90 Days (n = 281)	VTE ≤90 Days (n = 20)	P Value
Age, years, mean ± SD	57.7 ± 13.2	57.6 ± 13.4	59.1 ± 9.4	0.61
Female sex, number (%)	125 (41.5)	114 (40.6)	11 (5.0)	0.30
BMI, kg/m^2, mean ± SD	26.0 ± 4.5	25.9 ± 4.4	28.1 ± 5.8	0.04
Histology, number (%)				
AA	19 (6.3)	19 (6.8)	0 (0.0)	0.39
AOA	15 (5.0)	15 (5.3)	0 (0.0)	
AO	3 (1.0)	3 (1.1)	0 (0.0)	
GB	264 (87.7)	244 (86.8)	20 (100.0)	
WHO grade IV, number (%)	264 (87.7)	244 (86.8)	20 (100.0)	0.17
IDH1 mutation, number (%)	20 (10.0)	20 (10.6)	0 (0.0)	0.49
LOS, days, median (IQR)	7 (6–10)	8 (6–10)	7 (6–8)	0.31
Subtotal resection, number (%)	167 (55.5)	157 (55.9)	10 (50.0)	0.78
Awake surgery, number (%)	60 (20.8)	56 (20.7)	4 (21.1)	1.00
Operative time, minutes, median (IQR)	180 (130–240)	180 (120–240)	180 (180–200)	0.80
21 days LMWH, number (%)	135 (44.9)	123 (43.8)	12 (60.0)	0.24
Dexamethasone, number (%)	280 (93.0)	261 (92.9)	19 (95.0)	1.00
Postoperative KPS score ≥70, number (%)	171 (85.1)	158 (84.5)	13 (92.9)	0.65
Postoperative immobility, number (%)	22 (7.3)	18 (6.4)	4 (20.0)	0.07
History of VTE, number (%)	3 (1.0)	3 (1.1)	0 (0.0)	1.00
History of malignancy, number (%)	38 (12.7)	36 (12.9)	2 (10.0)	0.98
Radiotherapy, number (%)	273 (91.6)	254 (91.4)	19 (95.0)	0.88
Chemotherapy, number (%)	234 (78.5)	216 (77.7)	18 (90.0)	0.31

Multivariable Analysis

Predictor	OR	95% CI	P Value
BMI per 5 kg/m^2 increase	1.66	1.08–1.83	0.02
WHO grade IV	6.88	0.87–890.69	0.07
Postoperative immobility	4.15	1.15–13.03	0.03
21 days LMWH	2.19	0.88–5.75	0.09

VTE, venous thromboembolism; BMI, body mass index; AA, anaplastic astrocytoma; AOA, anaplastic oligoastrocytoma; AO, anaplastic oligodendroglioma; GB, glioblastoma; WHO, World Health Organization; LOS, length of stay; IQR, interquartile range; LMWH, low-molecular-weight heparin; KPS, Karnofsky performance scale; OR, odds ratio; CI, confidence interval.

et al.[9] started anticoagulation on the first day of radiotherapy and continued it up to 24 months after surgery. Smith et al.[6] administered LMWH during the period of hospitalization postoperatively and prolonged prophylaxis in high-risk patients only. However, the latter study was also underpowered, as it included only 25 patients who received prophylactic anticoagulation. Previous studies have found an association between the therapeutic use of anticoagulation and the incidence of ICH among patients with HGGs[31,33,34]; however, this has not been demonstrated yet for the prophylactic use of anticoagulation as well as the duration of this treatment. Lastly, immobility[2-4,17,18] and high BMI score[15] have already been identified as predictors of VTE in patients with HGGs.

The present study has several limitations. Patients were not randomly assigned to a prophylactic regimen. The duration of thromboprophylaxis was dependent on the timing of surgery and the surgeon's preference. Therefore, retrospectively dividing the cohort based on prophylactic regimen can introduce confounding by

Table 4. Univariable and Multivariable Analysis for Outcome of Postoperative Intracranial Hemorrhage

Univariable Analysis

Patient Characteristic	Total (n = 301)	No ICH (n = 292)	ICH (n = 9)	P Value
Operative time, minutes, median (IQR)	57.7 ± 13.2	57.6 ± 13.1	63.6 (14.0)	0.18
Female sex, number (%)	125 (41.5)	122 (41.8)	3 (33.3)	0.87
BMI, kg/m^2, mean ± SD	26.0 ± 4.5	26.0 ± 4.6	26.2 ± 2.1	0.90
Histology, number (%)				
AA	19 (6.3)	19 (6.5)	0 (0.0)	0.73
AOA	15 (5.0)	15 (5.1)	0 (0.0)	
AO	3 (1.0)	3 (1.0)	0 (0.0)	
GB	264 (87.7)	255 (87.3)	9 (100.0)	
WHO grade IV, number (%)	264 (87.7)	255 (87.3)	9 (100.0)	0.72
IDH1 mutation, number (%)	20 (10.0)	20 (10.4)	0 (0.0)	0.53
Subtotal resection, number (%)	167 (55.5)	161 (55.1)	6 (66.7)	0.73
Awake surgery, number (%)	60 (20.8)	60 (21.4)	0 (0.0)	0.25
Operative time, minutes, median (IQR)	180 (130–240)	180 (133–240)	180 (113–185)	0.36
21 days LMWH, number (%)	135 (44.9)	127 (43.5)	8 (88.9)	0.02
Dexamethasone, number (%)	280 (93.0)	271 (92.8)	9 (100.0)	0.87
History of VTE, number (%)	3 (1.0)	3 (1.0)	0 (0.0)	1.00
History of malignancy, number (%)	38 (12.7)	37 (12.8)	1 (11.1)	1.00

Multivariable Analysis

Predictor	OR	95% CI	P Value
Age per 10 years increase	1.40	0.81–2.67	0.26
21 days LMWH	9.67	1.73–180.95	0.03

ICH, intracranial hemorrhage; BMI, body mass index; AA, anaplastic astrocytoma; AOA, anaplastic oligoastrocytoma; AO, anaplastic oligodendroglioma; GB, glioblastoma; WHO, World Health Organization; LOS, length of stay; IQR, interquartile range; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval.

indication, and this can be a reason for the significant differences in baseline characteristics between the 2 groups (Table 1). We tried to reduce confounding by including all potential risk factors ($P < 0.20$) in the multivariable regression analysis; however, confounders that have not been measured or documented consistently could still influence the results. Owing to a low number of events, our study can be underpowered, especially for the occurrence of VTE within 21 days after surgery and ICH (both <5 events per variable in the multivariable analysis). Despite the low number of events, an association with the occurrence of ICH can still be observed, and the absolute VTE rates do not suggest a thromboprophylactic effect of continuing LMWH administration after discharge. Because all ICHs occurred within 10 days after surgery, it is questionable whether prolongation of thromboprophylaxis is responsible for all these events. Classification into prophylactic subgroups was based on the neurosurgeon performing the operation and the intention-to-treat as described in the postoperative orders; however, some minor degree of discrepancy between these orders and the actual postoperative management cannot be excluded. VTEs could have been missed if they were asymptomatic or diagnosed at other hospitals and not documented at our hospital. Given our practical research question, the relevance of asymptomatic cases of VTE is questionable, and missed cases owing to loss to follow-up are rare because patients were almost invariably followed in our own hospital. Lastly, as the subgroup of patients with grade III glioma consisted of only 37 patients, none of whom developed a thrombogenic or hemorrhagic event, it remains questionable to what extent the findings of the current study can be extrapolated to this subset of patients. Given the clinical, histologic, genomic, and therapeutic commonalities between grade III and IV gliomas as well as the lack of evidence on grade III gliomas, we deem the current findings relevant for both glioma subgroups; however, they should be interpreted within the clinical context of each individual patient.

We think that the limitations are inherently linked to a retrospective study design and proportionate to the strengths of

this study. This study focuses on the incidence of VTE in the short-term postoperative period, thereby reducing bias from either adjuvant therapy or a nonrepresentative group of survivors in the long-term period. To our knowledge, this study presents the largest sample of patients with HGGs prophylactically treated with LMWH after surgery among all studies that address the effect of prolonged thromboprophylaxis in patients with HGGs. Lastly, the difference in postoperative management between surgeons allows a relatively unbiased comparison between different postoperative strategies based on the duration of thromboprophylaxis.

The results of this study suggest that continuing LMWH beyond hospitalization is neither safe nor effective in preventing VTE. Therefore, we do not recommend prolongation of thromboprophylaxis up to 21 days after surgery routinely in every patient operated on for HGG. However, effectiveness of prolonged thromboprophylaxis targeted to high-risk patients cannot be excluded. Additionally, LMWH administered up to only 21 days can still be too short to achieve significant differences in VTE outcomes measured at 90 days after surgery. Multicenter prospective studies, preferably in a randomized setting, are needed to validate the findings of the current study. The development of VTE and ICH prediction models can help tailor postoperative management to the risk profile of the individual patient.

CONCLUSIONS

LMWH administration continued up to 21 days after craniotomy for HGG was not significantly associated with a lower VTE rate compared with prophylaxis until discharge (0–7 days). Prolonged prophylaxis was found to be associated with an increased risk of ICH. Based on our results, we do not recommend prolongation of prophylaxis beyond discharge routinely in every patient operated on for HGG. Future studies are needed to clarify the optimal timing of postoperative thromboprophylaxis and to identify patients with HGGs at risk for VTE and ICH.

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