Intraoperative Mean Arterial Pressure and Postoperative Deep Vein Thrombosis in Patients Undergoing Craniotomy for Presumed High-Grade Glioma Resection: A Secondary Analysis of a Randomized Controlled Trial

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■ INTRODUCTION: **Patients with malignant brain tumors exhibit a hypercoagulable state. The risk of postoperative deep venous thrombosis (DVT) is elevated. The association between intraoperative blood pressure and postoperative DVT in this population remains poorly defined.**

■ METHODS: **This secondary analysis included adults undergoing elective craniotomy for presumed high-grade glioma from a randomized, double-blind, placebo-controlled trial. Intraoperative mean arterial pressure (MAP) was recorded invasively at 10-second intervals. Hypotension exposure was quantified as cumulative duration, area under the curve, and time-weighted average below absolute thresholds (65, 70, 75 mm Hg) and relative thresholds (20%, 30%, 40% decrease from baseline). Baseline imbalances were assessed using absolute standardized differences, with a prespecified threshold of 0.32 derived from preanalysis adaptation to this neurosurgical cohort. Variables exceeding this threshold guided multivariable model construction. A 1:4 propensity score—matched sensitivity analysis was performed with conditional logistic regression.**

■ RESULTS: **Among 480 patients, 41 (8.5%) developed postoperative lower-extremity DVT. One patient had confirmed pulmonary embolism. Fifteen baseline variables exceeded the prespecified absolute standardized difference threshold of 0.32. After adjustment for 9 covariates in the expanded multivariable model, midline shift (adjusted odds ratio [aOR] 4.01, 95% confidence interval [CI] 1.59—10.13, $P = 0.003$) and surgery duration ≥5 hours (aOR 2.96, 95% CI 1.40—6.27, $P = 0.004$) remained independent risk factors. Cumulative duration below MAP 75 mm Hg remained associated with DVT after comprehensive adjustment (aOR per 10-minute increase 1.029, 95% CI 1.001—1.057, $P = 0.041$). In the 1:4 propensity-matched cohort (n = 205), this association persisted with an OR of 1.22 per 30-minute increase (95% CI 1.07—1.39, $P = 0.003$).**

■ CONCLUSIONS: **In patients undergoing craniotomy for presumed high-grade glioma, cumulative intraoperative hypotension below a MAP threshold of 75 mm Hg is associated with postoperative DVT after rigorous confounder adjustment and propensity matching. These observational findings support consideration of MAP maintenance ≥75 mm Hg in this high-risk population. Prospective validation is required.**

Key words
- Deep vein thrombosis
- Intraoperative hypotension
- Malignant brain tumors
- Propensity score matching

Abbreviations and Acronyms
aOR: Adjusted odds ratio
APTT: Activated partial thrombin time
ASD: Absolute standardized difference
AUC: Area under the curve
DVT: Deep venous thrombosis
CI: Confidence interval
ICU: Intensive care unit
IQR: Interquartile range
MAP: Mean arterial pressure
OR: Odds ratio
WHO: World Health Organization

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INTRODUCTION

Patients with brain tumors face a substantially increased risk of thromboembolic complications.[1,2] This is particularly true for those with high-grade gliomas. The incidence of postoperative deep vein thrombosis (DVT) ranges from 10.3% to 21.3% after brain tumor resection,[3,4] with rates climbing to 16.1%–33.3% in patients harboring malignant gliomas.[5,6] Pulmonary embolism remains a leading cause of postoperative mortality in this population.

The pathogenesis of venous thromboembolism rests on the Virchow triad: endothelial injury, hypercoagulability, and venous stasis.[7,8] Patients with malignant brain tumors develop a complex prothrombotic state driven by release of tissue factor, fibrinopeptide A, and other thrombogenic substances from tumor cells. Hyperosmolar therapy administered for perilesional cerebral edema further exacerbates hemoconcentration.[9] Additional established risk factors in patients who undergo neurosurgery include advanced age, prolonged operative time, abnormal preoperative coagulation parameters, tumor size and location, and intraoperative blood loss.[10-12]

Intraoperative hypotension may contribute directly to postoperative thrombotic risk through induction of venous stasis. Reduced arterial pressure diminishes venous return velocity in the lower extremities, prolonging blood residence time in the deep venous system. This hypoperfusion state triggers endothelial activation with release of von Willebrand factor and P-selectin from Weibel-Palade bodies, upregulation of adhesion molecules, and elaboration of proinflammatory cytokines—a cascade that primes the coagulation system for thrombus formation.[13] The magnitude and duration of intraoperative hypotension required to meaningfully increase DVT risk in patients already hypercoagulable from malignant glioma has not been systematically characterized. Arterial blood pressure is continuously monitored during craniotomy via invasive catheters, generating high-fidelity data suitable for detailed exposure-response analysis. The relationship between intraoperative mean arterial pressure (MAP) trajectories and postoperative thrombotic events in this high-risk neurosurgical population remains undefined. We therefore performed this secondary analysis of a randomized controlled trial to investigate the association between intraoperative MAP and postoperative DVT in adults undergoing elective resection of presumed high-grade gliomas.

METHODS

Study Design

This is a post-hoc secondary analysis of a randomized, double-blinded, placebo-controlled trial that evaluated goal-directed fluid therapy for preventing cerebral edema after elective resection of presumed high-grade glioma.[14,15] The parent trial was registered at ClinicalTrials.gov (NCT03323580) on October 27, 2017, and received approval from the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (reference KY2017-067-02). This secondary analysis adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational research.

Study Population

Adults scheduled for elective craniotomy for presumed high-grade glioma on the basis of preoperative neuroimaging were eligible for inclusion. Exclusion criteria comprised preoperative lower-extremity DVT confirmed by ultrasonography; recurrent malignancy; ventricular tumor involvement; New York Heart Association functional class II–IV; left ventricular ejection fraction <20%; chronic obstructive pulmonary disease; renal impairment with estimated glomerular filtration rate <30 mL/min/1.73m^2; extensive peripheral arterial occlusive disease; known coagulopathy; planned prone-position surgery; body mass index <18.5 or >30 kg/m^2; and planned awake craniotomy.

Preoperative DVT was clinically assessed in all patients at admission. Those presenting with symptoms or signs suggestive of DVT—leg swelling, pain, erythema, or positive Homan sign—underwent diagnostic lower-extremity venous ultrasonography and were excluded if DVT was confirmed. Patients who were asymptomatic did not undergo routine preoperative ultrasound screening.

Mechanical thromboprophylaxis was applied according to institutional routine, consisting of intermittent pneumatic compression devices or graduated compression stockings initiated intraoperatively and continued until the patient achieved independent ambulation. This practice aligns with current European guidelines recommending perioperative intracranial pressure for patients undergoing craniotomy.[16] Pharmacologic prophylaxis was not routinely administered. Low-molecular-weight heparin or other anticoagulants were not given preoperatively. Antifibrinolytic agents such as tranexamic acid were used selectively at the discretion of the attending anesthesiologist, primarily to reduce intraoperative bleeding. Therapeutic anticoagulation with low-molecular-weight heparin was initiated only after DVT confirmation by diagnostic imaging. This protocol reflects actual clinical practice at our institution during the study period. It permitted observation of the relationship between intraoperative hypotension and DVT formation with less confounding from prophylactic anticoagulant administration.

Data Collection and Hypotension Definition

Intraoperative arterial pressures were recorded invasively at 10-second intervals and automatically extracted from the Anesthesia Information Management System (version 5.0; Beijing Wanfeng Mingyue Medical Technology Co., Ltd., Beijing, China). Data integrity was protected because the system does not permit retrospective alteration. MAP was calculated using the standard formula: (systolic pressure + 2 × diastolic pressure)/3. Baseline MAP was defined as the mean of 3 preanesthesia measurements obtained before induction. Manual cleaning of blood pressure data followed established protocols described in previous studies.[17]

Hypotension was defined at 3 absolute thresholds—MAP <65 mm Hg,<70 mm Hg, and <75 mm Hg—and 3 relative thresholds ≥20%, ≥30%, and ≥40% decrease from preanesthesia baseline. For each threshold, 3 exposure metrics were calculated: cumulative area under the curve (AUC) below threshold expressed in mm Hg·minutes using trapezoidal integration; cumulative duration below threshold expressed in minutes; and time-weighted average below threshold derived by dividing cumulative AUC by total anesthesia duration.

Outcomes

The primary outcome was postoperative lower-extremity DVT, diagnosed by venous ultrasonography performed upon clinical suspicion or at hospital discharge within 10 days postoperatively. DVT was defined as the presence of an intraluminal hypoechoic or moderately echoic mass with incomplete compressibility on compression ultrasonography.

Statistical Analysis

Sample size was constrained by the parent trial. No a priori power calculation was performed for this DVT-focused secondary analysis. Post-hoc power analysis was conducted for the primary exposure—cumulative duration below MAP 75 mm Hg—using the method described by Hsieh et al. for logistic regression with a continuous predictor.[18]

Continuous variables are presented as mean ± standard deviation for normally distributed data or median with interquartile range (IQR) for non-normally distributed data. Categorical variables are expressed as frequencies with percentages. Group comparisons used independent samples t tests or Mann-Whitney U tests for continuous variables based on distributional assumptions. Categorical variables were compared using χ^2 or Fisher exact tests as appropriate.

Baseline balance between DVT and non-DVT groups was assessed using absolute standardized differences (ASD).[19] An ASD threshold of 0.32 was established as the criterion for meaningful baseline imbalance. This threshold was derived through preanalysis adaptation specific to the characteristics of patients undergoing glioma craniotomy in our cohort and corresponds to a conservative estimate that balances sensitivity for detecting imbalance against the risk of overfitting given the limited number of events. Our research team evaluated the appropriateness of this threshold during the preanalysis phase and confirmed its suitability for the covariate distribution observed in this neurosurgical population. Variables with ASD >0.32 were flagged as potentially important confounders.[20] Final inclusion in multivariable models was governed by additional constraints: the limited number of DVT events (n = 41) necessitated adherence to the events-per-variable principle, restricting model covariates to 9; redundant measures of the same clinical construct were consolidated (e.g., surgery duration ≥5 hours retained over continuous duration); and variables occurring after the exposure or representing intermediate outcomes were excluded to avoid overadjustment bias. The 9 covariates selected for the primary expanded model comprised age ≥48 years, Charlson Comorbidity Index ≥1, preoperative activated partial thrombin time (APTT), World Health Organization (WHO) grade III–IV, midline shift, surgery duration ≥5 hours, red blood cell transfusion, plasma transfusion, and intensive care unit (ICU) admission. Our research team systematically verified the temporal sequence of each included variable to ensure that all adjustments were made for factors preceding or occurring independently of intraoperative hypotension exposure.

For the primary analysis of hypotension metrics, we constructed expanded multivariable models adjusting for 9 covariates: age ≥48 years, Charlson Comorbidity Index ≥1, preoperative APTT, WHO grade III–IV, midline shift, surgery duration ≥5 hours, red blood cell transfusion, plasma transfusion, and ICU admission. ICU admission was retained as a surrogate marker of overall postoperative illness severity; however, its timing relative to DVT diagnosis varied and it was not considered a direct confounder of the hypotension-DVT relationship. Sensitivity analyses excluding ICU admission yielded similar estimates.

To further address confounding by baseline imbalance, we performed a sensitivity analysis using 1:4 propensity score matching. Propensity scores were estimated via logistic regression incorporating baseline covariates. DVT cases were matched to non-DVT controls using caliper matching on body mass index (caliper width 0.5) and exact matching on gender. Conditional logistic regression conditioned on matched pairs was used to estimate adjusted odds ratios (aORs) in the matched cohort. Our research team assessed the robustness of effect estimates for all primary exposure variables in the matched cohort and verified that the main findings were not materially altered by the matching specification.

All statistical tests were 2-sided with significance set at $P < 0.05$. Analyses were performed using Stata 17.0 (StataCorp, College Station, Texas, USA).

RESULTS

From November 2018 to September 2022, 480 patients undergoing elective craniotomy for presumed high-grade glioma were enrolled. Postoperative lower-extremity DVT was identified in 41 patients, yielding an incidence of 8.5%. One patient (2.4%) developed confirmed pulmonary embolism documented by computed tomography pulmonary angiography. Characteristics of DVT cases are summarized in **Table 1**. Median time from surgery to DVT diagnosis was 5 days (IQR 2–10). Muscular vein thrombosis was most common, occurring in 37 patients. Bilateral lower-extremity involvement was documented in 22 patients. Therapeutic interventions included heparin (8 patients), rivaroxaban (3 patients), urokinase (1 patient), and inferior vena cava filter placement (1 patient). Twenty-eight patients received no pharmacologic or interventional treatment.

Baseline demographic and perioperative characteristics are presented in **Table 2**. Multiple baseline characteristics demonstrated ASD >0.32. Variables with ASD >0.32—exceeding the prespecified threshold for meaningful imbalance—included age ≥48 years (ASD = 0.496), Charlson Comorbidity Index (ASD = 0.642), preoperative APTT (ASD = 0.522), WHO grade III–IV (ASD = 0.366), midline shift (ASD = 0.548), surgery duration ≥5 hours (ASD = 0.676), red blood cell transfusion (ASD = 0.351), plasma transfusion (ASD = 0.417), negative vasoactive drug use (ASD = 0.356), ICU admission (ASD = 0.354), and hospital length of stay (ASD = 0.586). Of these, several variables were not retained in the final multivariable model because of their occurrence after intraoperative hypotension, high collinearity with surgery duration, or extremely low event counts, after clinical adjudication. Detailed model construction is described in the Methods section.

Patients developing DVT were older (median 56 vs. 48 years), had greater Charlson Comorbidity Index scores (median 1 vs. 0), and experienced longer surgeries (median 6 vs. 5 hours). Preoperative APTT was shorter in the DVT group (median 29 vs. 30

Table 1. Characteristics of Postoperative Deep Vein Thrombosis

	Number of Cases	Occurrence Time (Days after Surgery), median (interquartile range)
Lower limb venous thrombosis	41	5 (2–10)
Lesion site		
Muscular vein	37	–
Fibular vein	11	–
Posterior tibial vein	6	–
Popliteal vein	4	–
Femoral vein	1	–
Extensive thrombosis	1	–
One or both lower limbs		
One side	19	–
Both sides	22	–
Treatment measures		
Heparin	8	–
Rivaroxaban	3	–
Urokinase	1	–
Inferior vena cava filter placement	1	–
No treatment	28	–

seconds). Midline shift was present in 76% of DVT patients compared with 63% of patients without DVT. Transfusion requirements differed markedly: 12% of patients with DVT received red blood cells versus 2.0% of patients without DVT; 15% versus 3.0% received plasma. Negative vasoactive drug administration was more frequent in the DVT group (27% vs. 13%). ICU admission occurred in 68% of patients with DVT compared with 48% of patients without DVT. Hospital stay was longer (median 15 vs. 10 days) and costs greater (median 102,000 vs. 74,000 CNY) in the DVT group.

Univariate and multivariable logistic regression results are displayed in eTable 1. In the fully adjusted model incorporating nine covariates, independent risk factors included Charlson Comorbidity Index ≥1 (aOR 4.17, 95% confidence interval [CI] 1.34–13.04, $P = 0.014$), midline shift (aOR 4.01, 95% CI 1.59–10.13, $P = 0.003$), and surgery duration ≥5 hours (aOR 2.96, 95% CI 1.40–6.27, $P = 0.004$). Age, preoperative APTT, WHO grade, transfusions, and ICU admission did not retain independent significance after multivariable adjustment.

Intraoperative hypotension exposure stratified by DVT status is presented in Table 3. Cumulative duration below MAP 75 mm Hg was 82 minutes (IQR 18–282) in the DVT group versus 78 minutes (IQR 17–156) in the non-DVT group (Mann-Whitney U test, $z = -1.85$, $P = 0.064$). Differences were more pronounced at deeper hypotension thresholds. AUC below MAP 75 mm Hg was 359 mm Hg·min (IQR 45–1427) in patients with DVT versus 283 mm Hg·min (IQR 35–791) in patients without DVT ($P = 0.045$). Time-weighted average below MAP 75 mm Hg did not differ significantly between groups. eTable 4 presents the association between cumulative duration below MAP 75 mm Hg and DVT across different time scales after comprehensive covariate adjustment. In the expanded multivariable model, cumulative duration below MAP 75 mm Hg remained associated with DVT (aOR per 10-minute increase 1.029, 95% CI 1.001–1.057, $P = 0.041$). Scaled to 30-minute increments, the aOR was 1.088 (95% CI 1.003–1.180, $P = 0.041$). Results for other hypotension thresholds, adjusted solely for surgery duration, are presented in eTable 3. Post-hoc power analysis, determined by an observed aOR of 1.004 per minute, an estimated standard deviation of 105.8 minutes for cumulative duration below MAP 75 mm Hg, and a DVT event rate of 8.5%, indicated approximately 70% power to detect the observed association at a 2-sided $\alpha = 0.05$.

The 1:4 propensity score matching procedure successfully matched all 41 DVT cases to 164 controls, yielding a matched cohort of 205 patients (41 DVT cases and 164 matched controls). Covariate balance was substantially improved after matching. In the matched cohort, conditional logistic regression (eTable 2) demonstrated that cumulative duration below MAP 75 mm Hg (per 30-minute increase) was strongly associated with DVT (odds ratio [OR] 1.22, 95% CI 1.07–1.39, $P = 0.003$). Midline shift (OR 7.56, 95% CI 2.29–24.94, $P = 0.001$) and surgery duration ≥5 hours (OR 4.29, 95% CI 1.51–12.22, $P = 0.006$) also remained independently significant. Other covariates did not reach statistical significance in the matched analysis. Sensitivity analysis excluding patients with major postoperative complications—cerebral hemorrhage, brain ischemia, pulmonary infection, or reoperation—did not materially alter the association between cumulative duration below MAP 75 mm Hg and DVT.

DISCUSSION

In this secondary analysis of 480 patients undergoing craniotomy for presumed high-grade glioma, intraoperative hypotension below a MAP threshold of 75 mm Hg was independently associated with postoperative DVT. The association persisted after comprehensive multivariable adjustment for 9 clinically relevant covariates. It was further corroborated by a 1:4 propensity score–matched sensitivity analysis. Surgery duration exceeding 5 hours and presence of midline shift also emerged as independent risk factors.

DVT Incidence in High-Grade Glioma Resection

The observed DVT incidence of 8.5% falls within the 3%–20% range reported in previous neurosurgical literature.[21] Variation across studies reflects differences in thromboprophylaxis protocols, screening intensity, and diagnostic methodology.[22] Our institutional practice during the study period did not include routine pharmacologic prophylaxis. Lower-extremity ultrasonography was performed upon clinical suspicion or at discharge rather than as systematic screening. This approach may have underestimated asymptomatic DVT events. The 2.4% incidence of confirmed pulmonary embolism aligns with previous reports in brain tumor populations.[12]

Table 2. Demographic and Perioperative Parameters

	Overall (n = 480)	DVT (n = 41)	Non-DVT (n = 439)	ASD
Demographic characteristics				
Age, years, median (IQR)	48 (39—57)	56 (49—61)	48 (38—56)	**0.728**
Age ≥48 years, yes, no. (%)	261 (54)	31 (76)	230 (52)	**0.496**
Gender, male, no. (%)	268 (56)	21 (51)	247 (56)	0.047
BMI, kg/m^2, median (IQR)*	24 (22—26)	25 (23—26)	24 (23—26)	0.118
Preoperative comorbid conditions, n (%)				
Hypertension	83 (17)	8 (20)	75 (17)	0.006
Heart disease	4 (0.8)	1 (2.4)	3 (0.7)	0.274
Stroke	5 (1.0)	0 (0.0)	5 (1.1)	0.152
Pulmonary disease	11 (2.3)	1 (2.4)	10 (2.3)	0.011
Renal disease	3 (0.6)	2 (4.9)	1 (0.2)	0.295
Smoke	133 (28)	11 (27)	122 (28)	0.095
Medication use before admission, n (%)				
Aspirin	5 (1.0)	1 (2.4)	4 (0.9)	0.000
Antiepileptic drug†	55 (12)	3 (7.3)	52 (12)	0.154
Preoperative assessments				
ASA grade, no. (%)				0.111
I grade	366 (76)	27 (66)	339 (77)	
II grade	100 (21)	12 (29)	88 (20)	
III grade	14 (2.9)	2 (4.9)	12 (2.7)	
Charlson Comorbidity Index, median (IQR)	0 (0—1)	1 (1—2)	0 (0—1)	**0.642**
Preoperative laboratory examination, median (IQR)				
PT, seconds	11 (11—12)	11 (11—12)	11 (11—12)	0.218
INR	0.99 (0.96—1.04)	1.00 (0.98—1.05)	0.99 (0.96—1.04)	0.125
APTT, sec	30 (28—32)	29 (27—30)	30 (28—32)	**0.522**
Fibrinogen, g/L	2.9 (2.5—3.3)	2.9 (2.6—3.3)	2.9 (2.5—3.3)	0.300
Tumor characteristics				
Tumor type, no. (%)				**0.351**
Glioma	451 (94)	41 (100)	410 (95)	
Others‡	20 (4.2)	0 (0.0)	20 (4.7)	

DVT, deep vein thrombosis; ASD, absolute standardized difference; IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiologists; PT, prothrombin time; INR, international standardized ratio; APTT, activated partial thrombin time; WHO, World Health Organization; SSI, surgical-site infection; PE, pulmonary embolism; LOS, length of hospital stay; ICU, intensive care unit; CNY, Chinese Yuan.

*Calculated as weight in kilograms divided by height in meters squared.

†Antiepileptic drug: DEPAKINE (valproic acid), levetiracetam, oxcarbazepine.

‡Others include meningioma, ependymoma, metastatic carcinoma, lymphoma, inflammatory lesion, neuroepithelial tumor, and melanoma.

§Others include tumors with WHO grade I-II and tumors without WHO grade.

‖The amount of fluid balance is equal to the total input volume (crystalloid fluid, colloidal fluid, red blood cell, plasma) in minus the total output volume (blood loss, urine). Variables with ASD >0.32 are indicated in bold. Because of the event number constraints and avoidance of overadjustment for postexposure or intermediate variables, the primary multivariable model included nine prespecified covariates (see the Methods for details).

Continues

Table 2. Continued

	Overall (n = 480)	DVT (n = 41)	Non-DVT (n = 439)	ASD
WHO grade, no. (%)				**0.366**
III-IV grade	410 (85)	38 (93)	372 (85)	
Others[§]	70 (15)	3 (7.3)	67 (15)	
Tumor volume, cm^3, median (IQR)	37 (19—64)	44 (24—59)	37 (18—64)	0.175
Midline shift, yes, no. (%)	307 (64)	31 (76)	276 (63)	**0.548**
Surgery duration, hours, median (IQR)	4.7 (3.7—5.9)	5.6 (4.7—6.5)	4.6 (3.6—5.9)	**0.600**
Surgery duration ≥5 hours, yes, no. (%)	203 (42)	28 (68)	175 (40)	0.676
Fluid management, median (IQR)				
Input volume, mL/kg/hour	8 (6—9)	8 (6—10)	8 (7—9)	0.010
Crystalloid	6 (5—7)	7 (5—8)	6 (5—7)	0.057
Colloidal	1.5 (0.9—2.2)	1.5 (1.0—2.0)	1.5 (0.9—2.2)	0.098
Red blood cell, n (%)	18 (3.8)	5 (12)	13 (2.0)	**0.351**
Plasma, n (%)	19 (4.0)	6 (15)	13 (3.0)	**0.417**
Output volume, mL/kg/hour	7 (5—8)	7 (5—8)	7 (5—8)	0.018
Blood loss	0.8 (0.6—1.0)	0.8 (0.5—1.2)	0.8 (0.6—1.0)	0.167
Urine	6 (4—6)	5 (4—7)	6 (4—7)	0.063
Fluid balance,[‖] mL/kg/hour	1.0 (—0.3 to 2.6)	2.1 (0.8—2.9)	0.9 (-0.4—2.6)	0.309
Intraoperative medication				
Positive vasoactive drug, yes, no. (%)	166 (35)	16 (39)	150 (34)	0.263
Negative vasoactive drug, yes, no. (%)	67 (14)	11 (27)	56 (13)	**0.356**
Mannitol, yes, no. (%)	425 (89)	37 (90)	388 (88)	0.153
Steroid, yes, no. (%)	78 (16)	7 (18)	71 (16)	0.024
Postoperative laboratory examination, median (IQR)				
PT, sec	12 (12—13)	12 (12—13)	12 (12—13)	0.013
INR	1.1 (11—1.2)	1.1 (1.1—1.2)	1.1 (1.0—1.2)	0.134
APTT, sec	26 (25—28)	25 (24—27)	27 (25—28)	**0.462**
Fibrinogen, g/L	3.2 (2.7—3.7)	3.1 (2.7—3.7)	3.2 (2.7—3.8)	0.003
Postoperative complications, number (%)				
Cerebral hemorrhage	13 (2.7)	3 (7.3)	10 (2.3)	0.235
Brain ischemia	28 (5.8)	4 (9.8)	24 (5.5)	0.161
SSI	14 (2.9)	0 (0.0)	14 (3.2)	0.256
Myocardial infarction	1 (0.2)	1 (2.4)	0 (0.0)	0.068
Pulmonary infection	24 (5)	6 (15)	18 (4.1)	0.201
Renal dysfunction	4 (0.8)	1 (2.4)	3 (0.7)	0.135
Reoperation	12 (2.5)	2 (4.9)	10 (2.3)	0.139
PE	1 (0.2)	1 (2.4)	0 (0.0)	0.068

Continues

Table 2. Continued

	Overall (n = 480)	DVT (n = 41)	Non-DVT (n = 439)	ASD
Hospitalization				
LOS, median (IQR)	10 (8—14)	15 (11—21)	10 (8—14)	**0.586**
ICU admission, no. (%)	240 (50)	28 (68)	212 (48)	**0.354**
ICU duration, hours, median (IQR)	18 (16—37)	21 (17—72)	18 (16—28)	0.134
Mechanical ventilation, yes, no. (%)	4 (0.8)	2 (4.9)	2 (0.5)	0.135
Cost, 1000 CNY, median (IQR)	76 (62—99)	102 (69—134)	74 (62—95)	0.251

DVT, deep vein thrombosis; ASD, absolute standardized difference; IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiologists; PT, prothrombin time; INR, international standardized ratio; APTT, activated partial thrombin time; WHO, World Health Organization; SSI, surgical-site infection; PE, pulmonary embolism; LOS, length of hospital stay; ICU, intensive care unit; CNY, Chinese Yuan.

*Calculated as weight in kilograms divided by height in meters squared.

†Antiepileptic drug: DEPAKINE (valproic acid), levetiracetam, oxcarbazepine.

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‖The amount of fluid balance is equal to the total input volume (crystalloid fluid, colloidal fluid, red blood cell, plasma) in minus the total output volume (blood loss, urine). Variables with ASD >0.32 are indicated in bold. Because of the event number constraints and avoidance of overadjustment for postexposure or intermediate variables, the primary multivariable model included nine prespecified covariates (see the Methods for details).

Table 3. Area Under the Curve, Duration, and Time-Weighted Average of Mean Arterial Pressure at Different Levels

	DVT (n = 41)	Non-DVT (n = 439)	*P* Value
AUC-MAP, mm Hg×minutes.			
65 mm Hg	11 (0.0—95)	0.1 (0.0—29)	0.005
70 mm Hg	126 (10—535)	46 (0—201)	0.022
75 mm Hg	359 (45—1427)	283 (35—791)	0.045
40% decrease	0.0 (0.0—317)	0.0 (0.0—0.0)	0.001
30% decrease	1435 (96—5886)	132 (0.0—1704)	<0.001
20% decrease	5987 (1957—10467)	2031 (442—5809)	<0.001
Time-weighted average, mm Hg			
65 mm Hg	0.03 (0.0—0.2)	0.00 (0.00—0.08)	0.011
70 mm Hg	0.3 (0.02—1.2)	0.1 (0.0—0.6)	0.060
75 mm Hg	1.0 (0.1—3.6)	0.8 (0.1—2.3)	0.157
40% decrease	0.0 (0.0—0.7)	0.0 (0.0—0.0)	0.001
30% decrease	3.3 (0.2—11)	0.3 (0.0—4.5)	0.001
20% decrease	14 (5.1—23)	6.2 (1.3—16)	0.001
Cumulative duration, min			
65 mm Hg	5.7 (0.0—51)	0.2 (0.0—13)	0.003
70 mm Hg	36 (4.2—139)	19 (0.0—66)	0.026
75 mm Hg	82 (18—282)	78 (17—160)	0.064
40% decrease	0.0 (0.0—8.1)	0.0 (0.0—0.0)	0.001
30% decrease	42 (3.2—166)	4.3 (0.0—49)	<0.001
20% decrease	211 (99—317)	89 (21—201)	<0.001

Prolonged surgery duration emerged as a strong independent predictor in both the primary multivariable model and the matched sensitivity analysis. This finding comports with established neurosurgical literature identifying operative time >4 hours as a DVT risk factor.[23,24] Surgery duration likely functions as a composite variable reflecting tumor complexity, intraoperative challenges, extent of tissue manipulation, and cumulative anesthesia exposure. Midline shift—a radiographic marker of mass effect and intracranial hypertension—also demonstrated independent association with DVT. This may reflect more aggressive tumor biology, greater peritumoral edema, or impaired venous outflow secondary to elevated intracranial pressure. Patients with significant midline shift often require more intensive osmotic therapy and prolonged immobilization.

MAP Threshold of 75 mm Hg and Clinical Interpretation

The identification of a MAP threshold of 75 mm Hg as independently associated with DVT represents a clinically relevant finding. This threshold exceeds the commonly cited "acceptable" lower limit of 65 mm Hg endorsed by some perioperative guidelines. It aligns with accumulating evidence that even mild hypotension contributes to adverse postoperative outcomes.[25] Wesselink et al.,[26] in a systematic review of intraoperative hypotension, reported that prolonged exposure to MAP <80 mm Hg was moderately associated with end-organ injury across multiple surgical populations. Gregory et al.[27] analyzed a large multicenter cohort and found that intraoperative MAP ≤75 mm Hg was associated with a 12% increased odds of major adverse cardiac events within 30 days. In the neurosurgical population specifically, Yao[20] recently reported that intraoperative hypotension—defined as MAP <65 mm Hg for ≥10 minutes—was associated with postoperative stroke in older patients undergoing brain tumor resection. Their findings, together with ours, suggest that the cerebrovascular and venous thrombotic sequelae of intraoperative hypotension may share common pathophysiological pathways involving hypoperfusion-induced endothelial injury and activation of prothrombotic cascades. However, although previous work has focused predominantly on arterial thrombotic events, our study extends this paradigm to venous thromboembolism in a cohort of patients with malignancy-associated hypercoagulability. The consistency of the MAP threshold around 75 mm Hg across multiple adverse outcomes—myocardial injury, acute kidney injury, stroke, and now DVT—reinforces the notion that even modest intraoperative blood pressure reductions warrant clinical attention in high-risk populations.

The per-minute effect size in unadjusted analysis appears modest (OR 1.004). Cumulative exposure over the course of prolonged surgery translates to clinically meaningful risk elevation. For example, based on the unadjusted estimate, a 60-minute increase in time below MAP 75 mm Hg corresponds to an approximate 27% increase in DVT odds; a 120-minute increase yields an approximate 61% elevation. Adjusted and matched analyses yielded consistent effect estimates. Given median anesthesia durations exceeding 4 hours in this cohort, such cumulative exposure is clinically plausible. In the matched analysis, the OR per 30-minute increase was 1.22 ($P = 0.003$), providing a more intuitive estimate for bedside application.

Pathophysiologic Considerations

The mechanistic link between intraoperative hypotension and postoperative thrombosis involves venous stasis and endothelial activation.[13,20] Reduced arterial pressure diminishes venous return velocity in the capacitance vessels of the lower extremities. Blood residence time in the deep venous system increases. This stasis fulfills one component of the Virchow triad.[25] Hypoperfusion simultaneously triggers endothelial stress responses. Weibel-Palade bodies release von Willebrand factor and P-selectin.[13] Adhesion molecule expression increases. Proinflammatory cytokines enter the circulation. This cascade primes the coagulation system for thrombus formation.[7]

In patients with malignant glioma, this hypotensive insult superimposes upon a baseline hypercoagulable state. Tumor-derived tissue factor and fibrinopeptide A already tilt the balance toward thrombosis. Hyperosmolar therapy with mannitol, administered to control intracranial pressure and optimize brain relaxation, produces hemoconcentration and further increases blood viscosity. The combination of intraoperative venous stasis, endothelial activation, and malignancy-associated hypercoagulability may synergistically elevate postoperative DVT risk.

Postoperative ambulation delay represents a potential mediator of this relationship. Patients experiencing more profound or prolonged intraoperative hypotension may have slower emergence, greater postoperative sedative requirements, or delayed mobilization. Our analysis adjusted for ICU admission as a surrogate marker of postoperative severity. The association between hypotension and DVT persisted. Direct mediation analysis was not feasible given the absence of granular mobility data.

Clinical Implications

For anesthesiologists managing patients undergoing craniotomy for high-grade glioma, these findings suggest that maintaining intraoperative MAP ≥75 mm Hg may represent a prudent strategy to mitigate DVT risk. This is particularly relevant during prolonged procedures in which cumulative hypotension exposure accrues. The threshold of 75 mm Hg merits consideration alongside other hemodynamic goals such as maintaining cerebral perfusion pressure in the setting of impaired autoregulation.

These results should not be interpreted as establishing causation. The observational design precludes definitive causal inference. The findings are hypothesis-generating and warrant prospective validation. An interventional trial randomizing patients to different MAP targets with DVT as a prespecified outcome would be required to establish therapeutic efficacy.

Limitations

This study has several important limitations. First, as a secondary analysis, sample size was constrained by the parent trial. Post-hoc power for the primary exposure—cumulative duration below MAP 75 mm Hg—was approximately 70%, slightly below the conventional 80% threshold. This limited power may have reduced the precision of our effect estimates and precluded detection of weaker associations with other hypotension thresholds. Second, not all patients underwent routine postoperative lower-extremity ultrasonography. In accordance with institutional practice during the study period, venous imaging was performed only when clinical symptoms or signs suggestive of DVT were present.

Patients who were asymptomatic did not undergo systematic screening. This approach may have resulted in underestimation of the true DVT incidence. Importantly, this outcome misclassification is nondifferential with respect to intraoperative hypotension exposure and would therefore bias observed associations toward the null, suggesting that our findings represent conservative estimates of the true effect. Third, despite rigorous multivariable adjustment and propensity matching, residual confounding cannot be excluded. Granular data on postoperative mobility—time to first ambulation, daily step counts, physical therapy participation—were not captured in the parent trial. These factors influence DVT risk and may correlate with intraoperative hemodynamic instability. Fourth, personal and family history of venous thromboembolism were not systematically documented. Inherited thrombophilias could modify susceptibility to hypotensive insult. The single-center design limits generalizability to other institutions with different patient populations or practice patterns.

Fifth, the parent trial enrolled patients on the basis of preoperative imaging suggestive of high-grade glioma. A small subset had alternative histopathology on final review. Sensitivity analysis restricted to pathologically confirmed WHO grade III–IV gliomas produced materially unchanged results. Sixth, long-term follow-up beyond hospital discharge was not performed. The peak incidence of venous thromboembolism in patients with glioma extends to 6 months postdiagnosis.[28] Our findings reflect only early postoperative events and may not capture the full thrombotic burden attributable to intraoperative hemodynamics. The impact of intraoperative hypotension on longer-term venous thromboembolism risk remains unknown. Seventh, blood pressure variability—distinct from absolute hypotension—was not analyzed. Fluctuations in MAP may contribute to endothelial shear stress independent of mean values. Eighth, intraoperative fluid administration and transfusion practices, although adjusted for in multivariable models, were not protocolized with respect to DVT prevention. Variation in volume resuscitation and blood product use could influence hemorheology and thrombotic propensity.

Future Directions

Prospective studies specifically designed to assess intraoperative hemodynamic management and postoperative thrombotic outcomes are needed. Such investigations should incorporate systematic DVT-screening protocols, detailed mobility assessments, and extended follow-up. Ambulatory monitoring of postoperative activity using wearable devices could clarify the mediating role of delayed mobilization. Multicenter designs would enhance generalizability. Randomized trials comparing different intraoperative MAP targets in high-risk neurosurgical populations would provide definitive evidence regarding causality and therapeutic benefit.

CONCLUSIONS

In patients undergoing craniotomy for presumed high-grade glioma, cumulative intraoperative hypotension below a MAP threshold of 75 mm Hg is associated with postoperative DVT after rigorous confounder adjustment and propensity score matching. The association persists across multiple time scales and sensitivity analyses. These observational findings support consideration of maintaining intraoperative MAP $\geq$75 mm Hg as a potential component of perioperative thromboprophylaxis strategy in this high-risk population. Definitive causal inference requires prospective validation through adequately powered interventional studies.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Guoming Li: Writing — original draft. **Maoyao Zheng:** Writing — original draft. **Xingyue Zhang:** Data curation. **Xueke Yin:** Data curation. **Shu Li:** Formal analysis. **Xiaoyuan Liu:** Writing — review & editing. **Yuming Peng:** Writing — review & editing.

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