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Effect of perioperative aspirin use on hemorrhagic complications in elective craniotomy for brain tumors: results of a single-center, retrospective cohort study

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OBJECTIVE In daily practice, neurosurgeons face increasing numbers of patients using aspirin (acetylsalicylic acid, ASA). While many of these patients discontinue ASA 7–10 days prior to elective intracranial surgery, there are limited data to support whether or not perioperative ASA use heightens the risk of hemorrhagic complications. In this study the authors retrospectively evaluated the safety of perioperative ASA use in patients undergoing craniotomy for brain tumors in the largest elective cranial surgery cohort reported to date.

METHODS The authors retrospectively analyzed the medical records of 1291 patients who underwent elective intracranial tumor surgery by a single surgeon from 2007 to 2017. The patients were divided into three groups based on their perioperative ASA status: 1) group 1, no ASA; 2) group 2, stopped ASA (low cardiovascular risk); and 3) group 3, continued ASA (high cardiovascular risk). Data collected included demographic information, perioperative ASA status, tumor characteristics, extent of resection (EOR), operative blood loss, any hemorrhagic and thromboembolic complications, and any other complications.

RESULTS A total of 1291 patients underwent 1346 operations. The no-ASA group included 1068 patients (1112 operations), the stopped-ASA group had 104 patients (108 operations), and the continued-ASA group had 119 patients (126 operations). The no-ASA patients were significantly younger (mean age 53.3 years) than those in the stopped- and continued-ASA groups (mean 64.8 and 64.0 years, respectively; p < 0.001). Sex distribution was similar across all groups (p = 0.272). Tumor locations and pathologies were also similar across the groups, except for deep tumors and schwannomas that were relatively less frequent in the continued-ASA group. There were no differences in the EOR between groups. Operative blood loss was not significantly different between the stopped- (186 ml) and continued- (220 ml) ASA groups (p = 0.183). Most importantly, neither hemorrhagic (0.6%, 0.9%, and 0.8%, respectively; p = 0.921) nor thromboembolic (1.3%, 1.9%, and 0.8%; p = 0.779) complication rates were significantly different between the groups, respectively. In addition, the multivariate model revealed no statistically significant predictor of hemorrhagic complications, whereas male sex (odds ratio [OR] 5.9, 95% confidence interval [CI] 1.7–20.5, p = 0.005) and deep-extraaxial-benign ("skull base") tumors (OR 3.6, 95% CI 1.3–9.7, p = 0.011) were found to be independent predictors of thromboembolic complications.

CONCLUSIONS In this cohort, perioperative ASA use was not associated with the increased rate of hemorrhagic complications following intracranial tumor surgery. In patients at high cardiovascular risk, ASA can safely be continued during elective brain tumor surgery to prevent potential life-threatening thromboembolic complications. Randomized clinical trials with larger sample sizes are warranted to achieve a greater statistical power.

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KEYWORDS aspirin; acetylsalicylic acid; hemorrhage; thromboembolism; brain tumor; craniotomy; vascular disorders

In daily practice, neurosurgeons face an increasing number of patients taking aspirin (acetylsalicylic acid, ASA) due to its use for primary prevention in aging populations[31] and for reducing the risk of stroke or other thromboembolic disease in patients with heightened risk. While ASA is commonly discontinued in such patients 7–10 days before any elective intracranial surgery,[5,20] there is only anecdotal evidence and no strong data to support whether or not there is heightened risk of hemorrhagic complications associated with perioperative ASA continuation.[23]

Each year, approximately 3 million individuals worldwide undergo percutaneous coronary intervention. It is estimated that approximately 7%–17% of them will require noncardiac surgery within a year of stent implantation.[5] In these patients, antiplatelet therapy interruption may expose patients to the potential risks of stent thrombosis, perioperative myocardial infarction, or cardiovascular death.[3,5,7] In addition, growing evidence suggests that perioperative withdrawal of ASA used for secondary stroke prevention increases thromboembolic risk.[2] Therefore, in high-risk patients, most guidelines recommend continuation of ASA during the perioperative period of noncardiac surgery.[19,27] However, intracranial surgery appears to be an exception, at least in practice, due to potentially deadly hemorrhagic complications.[5,20]

We hypothesized that continuing ASA in high-risk patients, when combined with meticulous microsurgical techniques, adequate hemostasis, and good perioperative care, does not significantly elevate the risk of serious intracranial bleeding, but indeed prevents thromboembolic complications. Hence, the research questions we aimed to answer in this study were: 1) does the risk of hemorrhagic complications increase in patients who continue ASA use; and 2) does the risk of thromboembolic complications increase in patients who have not taken ASA or who have discontinued taking ASA? Therefore, in this retrospective study, we evaluated the safety of perioperative ASA use in patients undergoing elective craniotomy for brain tumors; this report is the largest neurosurgical cohort study of this type that we are aware of.

Methods

Study Design

This retrospective cohort study analyzed the medical records of all consecutive patients undergoing elective intracranial tumor surgery by a single surgeon between 2007 and 2017 at the University of Wisconsin Hospital. This study of the effects of ASA on intracranial tumor surgery was evaluated and approved by the IRB of the University of Wisconsin School of Medicine and Public Health. As a retrospective study, and one that does not reveal individual patient information, patient consent was not required.

Inclusion and Exclusion Criteria

The study inclusion criteria were as follows: 1) elective craniotomy for tumor surgery; 2) known ASA status; and 3) complete data regarding complications. The exclusion criteria were: 1) patients who had started ASA on admission or perioperatively for the first time; and 2) incomplete or indeterminate data regarding ASA status and/or complications ascribed to ASA.

Study Groups

The patients were divided into three groups based on perioperative ASA status, as named and described as follows: 1) group 1, no ASA, patients with no regular preoperative ASA use; 2) group 2, stopped ASA, patients had discontinued ASA at least 7 days prior to elective tumor surgery; and 3) group 3, continued ASA, patient continued ASA through pre-, intra-, and postoperative periods.

The decision to continue or stop ASA treatment was made based on the thromboembolic risk level of the individual patient. As a general rule, patients who were at high risk for thromboembolic complications underwent surgery while on ASA, whereas it was withdrawn in those patients at low cardiovascular risk. Risk assessments were based on international guidelines[13,22,33] and performed in conjunction with relevant consultations (cardiology, neurology, anesthesiology). Management of perioperative ASA therapy was determined by a consensus of the surgeon, anesthesiologist, cardiologist, neurologist, and patient.

Primary prevention was defined as ASA use in patients with risk factors who had not yet developed clinically manifest cardiovascular disease, coronary artery disease, or peripheral vascular disease. Some primary prevention patients were considered to have a potentially higher cardiovascular risk when there were well-known coexistent factors such as diabetes, kidney failure, advanced age, male sex, higher systolic blood pressure, and total blood cholesterol.

Secondary prevention was aimed at preventing recurrent cardiovascular events in patients with established cardiovascular disease including angina pectoris, coronary heart disease, myocardial infarction, transient ischemic attacks, cerebrovascular disease, and peripheral vascular disease, or after coronary artery angioplasty and stenting/bypass surgery or carotid artery stenting/endarterectomy. A recent history of established cardiovascular events and/or revascularization procedures (such as angioplasty/stent/bypass/endarterectomy) was considered high risk. Finally, in addition to using ASA for atherosclerotic cardiovascular diseases, some patients used ASA prophylactically due to secondary venous thromboembolism risk, and these patients continued ASA if their risk was assessed as sufficiently high.

ASA was continued in all high-risk patients under primary and secondary prevention, but discontinued in patients at low cardiovascular risk. Regardless of the indication and ASA status, other antiaggregants (e.g., clopidogrel) and anticoagulants were discontinued before operations. All patients were managed with the same hemostasis protocol, including meticulous intraoperative hemostasis with topical hemostatic agents and strict perioperative blood pressure control.

Data Collection

The following data were collected using electronic health records: age, sex, medical history, ASA status, ASA dose, indication for ASA, tumor location, pathology, tumor

extent of resection (EOR), estimated blood loss, and any complications within 30 days of surgery. Indications for ASA use were detailed and grouped into primary and secondary prevention categories. Complications were divided into three groups: hemorrhagic, thromboembolic, and other. Hemorrhagic and thromboembolic complications were further divided into intracranial and extracranial subgroups. ASA status and complications were verified by two neurosurgeons who were not involved in patient management and who were blinded to the study.

Statistical Analysis

Statistical analyses were performed using SPSS (version 22.0, IBM Corp.). Data are presented as means ± standard deviations for parametric variables, median (range) for nonparametric continuous variables, and percentage (95% confidence interval [CI]) for categorical variables. One-way ANOVAs with Bonferroni correction and Kruskal-Wallis tests were used for multiple-group comparisons of parametric and nonparametric variables, respectively. Binomial CIs were calculated for proportions. The Student t-test was used for continuous variables, and chi-square and Fisher's exact tests for categorical variables to compare between

two groups. Factors with a p value < 0.1 in univariate analysis were introduced into the multivariate model. Highly correlated variables were combined into a single variable before entering the multivariate model. Multivariate analysis was performed using a logistic regression model. A p value < 0.05 was considered statistically significant.

Results

Demographic Features

A total of 1291 patients underwent 1346 operations for intracranial tumor resection. The mean age at presentation was 55.2 ± 15.3 years. The no-ASA group patients were significantly younger than those in the stopped-ASA and continued-ASA groups: 53.3 vs 64.8 vs 64.0 years old, respectively (p < 0.001). Patient sex was nearly equally distributed overall (51% female, 49% male) and within each of the ASA status groups (p = 0.272; Table 1).

ASA Status and Indications

The no-ASA group included 1068 patients (1112 operations), the stopped-ASA group had 104 patients (108 operations), and the continued-ASA group had 119 patients

TABLE 1. Demographic, tumor, and surgical characteristics of the patients

| Variable | All | ASA Group | | | p Value |
		None	Stopped	Continued	
No. of patients	1291	1068	104	119	
No. of operations	1346	1112	108	126	
Mean age ± SD, yrs	55.2 ± 15.3	53.3 ± 15.3	64.8 ± 9.6	64.0 ± 12.3	**<0.001**
Males	656 (49)	531 (48)	59 (55)	66 (52)	0.272
Females	690 (51)	581 (52)	49 (45)	60 (48)	
Tumor type					
Astrocytoma	350 (26)	288 (26)	23 (21)	39 (31)	0.186
Meningioma	331 (25)	262 (24)	32 (30)	37 (29)	0.161
Metastatic	199 (15)	156 (14)	22 (20)	21 (17)	0.234
Schwannoma	227 (17)	203 (18)	13 (12)	11 (9)	**0.017**
Pituitary adenoma	59 (4)	41 (4)	7 (7)	11 (9)	**0.016**
Other	180 (13)	162 (15)	11 (10)	7 (6)	**0.008**
Tumor grade					
Benign	825 (61)	688 (62)	67 (62)	70 (56)	0.394
Malignant	521 (39)	424 (38)	41 (38)	56 (44)	
Tumor location					
Supratentorial	954 (71)	777 (70)	77 (71)	100 (80)	0.084
Infratentorial	392 (29)	335 (30)	31 (29)	26 (21)	
Deep	762 (57)	641 (58)	63 (58)	58 (46)	**0.042**
Superficial	584 (43)	471 (42)	45 (42)	68 (54)	
Intraaxial	763 (57)	635 (57)	54 (50)	74 (59)	0.323
Extraaxial	583 (43)	477 (43)	54 (50)	52 (41)	
EOR					
Gross-total	1045 (78)	862 (78)	86 (80)	97 (77)	0.911
Near-total	105 (8)	87 (8)	6 (6)	12 (10)	
Subtotal	162 (12)	133 (12)	14 (13)	15 (12)	
Biopsy	34 (3)	30 (3)	2 (2)	2 (2)	

Data given as number and percentage of total (%) per operation unless otherwise indicated. Boldface type indicates statistical significance.

TABLE 2. Aspirin doses and indications in patients using ASA (groups 2 and 3)

Variable	ASA Group			p Value
	Stopped	Continued	Stopped + Continued	
No. of patients	104	119	223	
No. of operations	108	126	234	
ASA doses, mg				
81	85 (79)	96 (76)	181 (77)	0.647
162	5 (5)	3 (2)	8 (3)	0.345
325	18 (17)	27 (21)	45 (19)	0.357
ASA indications				
Arterial thromboembolism	19 (18)	44 (35)	62 (26)	**0.003**
Venous thromboembolism	4 (4)	9 (7)	13 (6)	0.252
Arterial + venous thromboembolism	0 (0)	2 (2)	2 (1)	NA
Primary prevention	85 (79)	71 (56)	151 (65)	**<0.001**
Arterial thromboembolism				
Coronary artery disease	10 (9)	38 (30)	48 (21)	**<0.001**
Stent	5 (5)	5 (4)	10 (4)	
Coronary artery bypass graft	1 (1)	2 (2)	3 (1)	
Peripheral vascular disease	6 (6)	16 (13)	21 (9)	0.061
Stroke	3 (3)	5 (4)	7 (3)	0.617
Atrial fibrillation & pacemaker	3 (3)	7 (6)	10 (4)	0.294
Venous thromboembolism				
Pulmonary embolism	1 (1)	4 (3)	5 (2)	0.236
Deep venous thrombosis	4 (4)	7 (6)	11 (5)	0.505

NA = not applicable.
Data given as number and percentage of total (%) per operation unless otherwise indicated. Boldface type indicates statistical significance.

(126 operations). Most patients (77%) used 81 mg of ASA, whereas 19% were taking 325 mg. Seventy-nine percent of the patients in the stopped-ASA group, and 56% in the continued-ASA group, were taking ASA for primary prevention. Of those patients taking ASA for primary prevention, all in the continued-ASA group, but only a small fraction (10%) of the stopped-ASA group, had a high estimated cardiovascular risk. Coronary artery disease was the leading reason for ASA use for secondary prevention (Table 2).

Tumor Location

Tumor location was classified as supra- or infratentorial, deep or superficial, or intra- or extraaxial based on preoperative radiological imaging (Tables 1 and 3). Most tumors were supratentorial (71%). Overall, deep tumors (57%) were slightly more frequent than superficial (43%), and intraaxial tumors (57%) were slightly more frequent than extraaxial tumors (43%). When evaluated based on these three factors together, the most common tumors were located at the superficial cortex/subcortex (38%) followed by the cerebellopontine angle (20%) and the anterior-middle skull base (17%). Between-group analysis showed that deep tumors were relatively less common in the continued-ASA group (46%) in comparison to the no-ASA group (58%) and the stopped-ASA group (58%; p = 0.042), whereas all the ASA status groups were similar in terms of other location categories (e.g., supra- vs infratentorial, intra- vs extraaxial).

Tumor Pathology

Benign tumors constituted 61% of tumors. Distribution of malignant and benign tumors was similar across the groups (p = 0.394). The most common tumor types (astrocytoma, meningioma, and metastatic) were present in similar percentages among the ASA status groups. However, there were significantly fewer schwannomas in the continued-ASA group and fewer pituitary adenomas in the no-ASA group.

Extent of Resection

Overall, gross-total resections were achieved for 78% of patients, with no significant difference between ASA status groups. Likewise, the groups also had similar percentages of near-total and subtotal resection, and biopsy.

Operative Blood Loss

Mean estimated blood loss during the surgery was similar between the stopped-ASA group (mean 186 ± 201 ml, median 150 ml) and the continued-ASA group (mean 220 ± 185 ml, median 200 ml; p = 0.183). Only 6.5% in the stopped-ASA group and 8.7% in the continued-ASA group had operative blood loss greater than 500 ml.

Complications

Complications were rare in the entire study cohort, occurring in only 5% of cases (Fig. 1, Tables 4 and 5). There were no significant differences between the groups in

TABLE 3. Details of tumor locations in patients

Tumor Location	ASA Group None	Stopped	Continued	Total	p Value
Intraventricular	21 (2)	2 (2)	0 (0)	23 (2)	NA
Fourth ventricle	14 (1)	0 (0)	0 (0)	14 (1)	NA
Anterior-middle skull base	176 (16)	25 (23)	28 (22)	229 (17)	**0.041**
Cerebellar	44 (4)	4 (4)	7 (6)	55 (4)	0.676
Cerebellopontine angle	223 (20)	23 (21)	15 (12)	261 (19)	0.079
Deep cortical	107 (10)	7 (7)	9 (7)	123 (9)	0.399
Posterior-middle skull base	48 (4)	4 (4)	4 (3)	56 (4)	0.806
Superficial cortex	413 (37)	40 (37)	59 (47)	512 (38)	0.103
Parasagittal-parafalcine	14 (1)	1 (1)	2 (2)	17 (1)	0.903
Deep extraaxial	16 (1)	1 (1)	1 (1)	18 (1)	0.776
Deep nuclei	30 (3)	1 (1)	1 (1)	32 (2)	0.242
Brainstem	6 (1)	0 (0)	0 (0)	6 (1)	NA
Supratentorial	777 (70)	77 (71)	100 (80)	954 (71)	0.084
Infratentorial	335 (30)	31 (29)	26 (21)	392 (29)	
Deep	641 (58)	63 (58)	58 (46)	762 (57)	**0.042**
Superficial	471 (42)	45 (42)	68 (54)	584 (43)	
Intraaxial	635 (57)	54 (50)	74 (59)	763 (57)	0.323
Extraaxial	477 (43)	54 (50)	52 (41)	583 (43)	
Supratentorial/deep/intraaxial	158 (14)	10 (9)	10 (8)	178 (13)	0.064
Supratentorial/deep/extraaxial	192 (17)	26 (24)	29 (23)	247 (18)	0.079
Supratentorial/superficial/intraaxial	413 (37)	40 (37)	59 (47)	512 (38)	0.103
Supratentorial/superficial/extraaxial	14 (1)	1 (1)	2 (2)	17 (1)	0.903
Infratentorial/deep/intraaxial	20 (2)	0 (0)	0 (0)	20 (1)	NA
Infratentorial/deep/extraaxial	271 (24)	27 (25)	19 (15)	317 (24)	0.062
Infratentorial/superficial/intraaxial	44 (4)	4 (4)	5 (4)	53 (4)	0.991
Infratentorial/superficial/extraaxial	0 (0)	0 (0)	2 (2)	2 (0.1)	NA

Data given as number and percentage of total (%) per operation unless otherwise indicated. Boldface type indicates statistical significance.

terms of overall complication rates (no-ASA: 4.9%, 95% confidence interval [CI] 3.7–6.3; stopped-ASA: 4.6%, 95% CI 1.5–10.5; continued-ASA: 2.4%, 95% CI 0.5–6.8; p = 0.454). We categorized complications as hemorrhagic, thromboembolic, and other. Hemorrhagic complications were observed in less than 1% of the operations. There were no significant differences between the groups (no-ASA: 0.6%, 95% CI 0.3–1.3; stopped-ASA: 0.9%, 95% CI 0.0–5.1; continued-ASA: 0.8%, 95% CI 0.0–4.3; p = 0.921). Only 1 patient in the continued-ASA group had intracranial hemorrhage due to an epidural hematoma. Intracranial hemorrhages were more common than extracranial hemorrhages (8 patients vs 1 patient). Six patients had intracerebral hematomas and 2 patients had epidural hematomas. In summary, there were no significant differences in hemorrhagic complications between the different ASA status conditions (Table 4, Fig. 1).

Thromboembolic complications were twice as common as hemorrhagic complications (18 vs 9 patients), although ASA status made no statistical difference (no-ASA: 1.3%, 95% CI 0.8–2.2; stopped-ASA: 1.9%, 95% CI 0.2–6.5; continued-ASA: 0.8%, 95% CI 0.0–4.3; p = 0.779). Nine patients had deep venous thrombosis, 8 had pulmonary embolism, and 1 patient had an ischemic stroke. As shown in Fig. 1 and Table 4, any differences in thromboembolic complications were insignificant.

Other complications not directly related to hemorrhagic or thromboembolic events included cerebral spinal fluid fistulas, pulmonary problems, postoperative brain edema, and infectious complications. All were rare (2.6%) in the study cohort. The no-ASA group had the highest rate (2.9%, 95% CI 2.0–4.0) followed by the stopped-ASA group (1.9%, 95% CI 0.2–6.5) and the continued-ASA group (0.8%, 95% CI 0.0–4.3). However, as shown in Fig. 1 and Table 4, any differences in these other complications with respect to ASA status were insignificant.

Predictors of Hemorrhagic and Thromboembolic Complications

We studied potential predictors of both hemorrhagic and thromboembolic complications in the entire study cohort regardless of ASA status. First, we evaluated the effects of demographic, tumor, and surgical features using univariate analysis (Table 5). For hemorrhagic complications, the only factor that may have had a marginal effect on outcomes was the intraaxial tumor location (p = 0.087). However, for thromboembolic complications, male sex was found to be significantly associated with increased risk (p
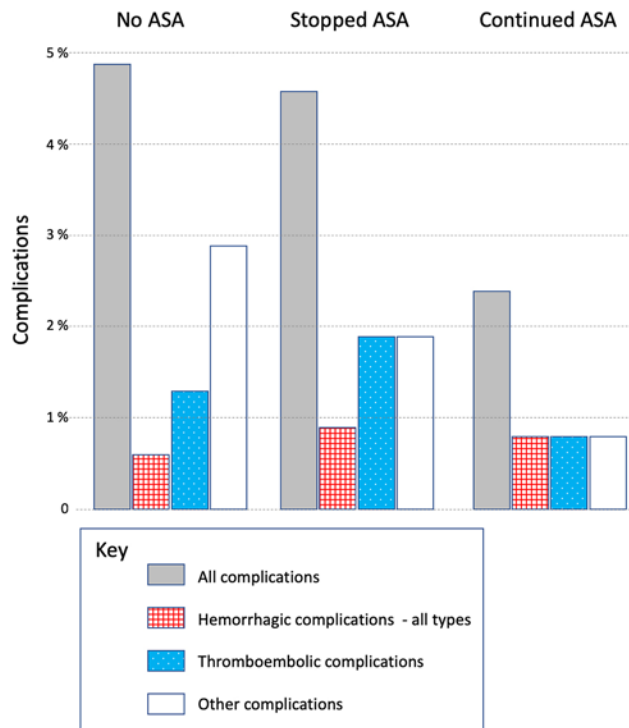
FIG. 1. Complication rate (percentage) per ASA condition. There are no significant differences in any complication category between groups (p > 0.05). Figure is available in color online only.

= 0.003). Other factors with marginal effects were benign (p = 0.053), deep (p = 0.092), and extraaxial (p = 0.055) tumors. Because these three factors showed a high multicollinearity, we combined three factors into a single variable (deep-extraaxial-benign tumors, or mostly "skull base" tumors) and then entered this into the multivariate model. Whereas the multivariate model yielded no statistically significant predictor of hemorrhagic complications, it revealed that both male sex (odds ratio [OR] 5.9, 95% CI 1.7–20.5, p = 0.005) and deep-extraaxial-benign (skull base) tumors (OR 3.6, 95% CI 1.3–9.7, p = 0.011) were independent predictors of thromboembolic complications. As expected, ASA status did not have any effect on either hemorrhagic or thromboembolic complications.

Discussion

We observed that perioperative ASA use does not increase hemorrhagic complications in elective intracranial tumor surgery, so long as a strict perioperative protocol is used that provides meticulous intraoperative hemostasis. In addition, there were no significant differences in thromboembolic complications between the no-, stopped-, and continued-ASA groups, despite their different cardiovascular risk levels. This finding may further suggest that ASA continuation may have indeed prevented some thromboembolic complications in patients whose ASA was not stopped perioperatively due to their high cardiovascular risk. Taken together, this retrospective study challenges the belief that ASA should be discontinued before elective intracranial surgery. This study thus provides a justification for future

randomized clinical trials to establish actual risks and benefits of cranial surgery while taking ASA.

With increasing life expectancy and availability of healthcare services worldwide, physicians, including neurosurgeons, face more and more patients with advanced age and comorbidities.[3,12,31] Thromboembolic events, including heart attack and stroke, are by far the leading causes of death and disability globally.[12] Both primary and secondary prevention of these thromboembolic events require antiplatelet and/or anticoagulant therapies.[3] Therefore, the number of people receiving ASA is increasing drastically.[34] In 2005, about one-fifth of US adults (age 18 and older) reported taking ASA either every day or every other day. ASA use increases with age, so that almost half of those age 65 and over take ASA regularly.[30] A more recent nationwide survey of US adults aged 45–75 years found that 52% of the respondents were taking ASA regularly.[31]

ASA therapy reduces subsequent mortality when used following myocardial infarction (MI), coronary revascularization, or stroke.[19] Of the approximately 3 million individuals undergoing percutaneous coronary intervention annually, approximately 7%–17% require a noncardiac surgery within a year of stent implantation.[4] Patients undergoing noncardiac surgery are also at risk of postoperative major vascular complications (i.e., vascular death, nonfatal MI, nonfatal cardiac arrest, and nonfatal stroke), and MI is the most common major complication. An estimated 6–10 million patients will suffer an MI during the perioperative period.[24] Discontinuation of antiplatelet therapy is an important factor for stent thrombosis.[4] In addition, growing evidence suggests that perioperative withdrawal of ASA for secondary stroke prevention increases thromboembolic risk.[2]

Observational studies suggest that the discontinuation of ASA before noncardiac surgery results in an increased thrombotic risk.[7,15] In contrast, a large international randomized placebo-controlled trial (POISE-2) showed that perioperative ASA use (200 mg) had no significant effect on the rate of death or nonfatal MI but increased the risk of major bleeding.[11] However, as the authors argued, there might be zero effect of major bleeding on the prevention of MI through supply-demand mismatch of myocardial oxygen due to bleeding or another mechanism of perioperative MI other than coronary artery thrombus. Additionally, there are a number of methodological issues regarding the design of the POISE-2 trial that question the validity and generalizability of the conclusions.[14] This study used 200 mg of ASA instead of the typical low-dose 75–100 mg of ASA used worldwide. In addition, this trial evaluated continuation of ASA versus de novo initiation of ASA therapy in patients undergoing noncardiac surgery and provides no data on the risks of stopping ASA in patients with coronary stents or at high cardiovascular risk. Largely influenced by the POISE-2 trial, a recent meta-analysis pooling of all relevant studies to date showed no benefits to survival, no changes in cardiovascular mortality and arterial ischemic events, an increase in major bleedings, but, interestingly, a reduction in venous thromboembolic events with ASA.[32] Taken together, these data suggest that major bleeding is likely a significant contributor of perioperative mortality and arterial ischemic events, albeit indirectly. Therefore,

TABLE 4. Hemorrhagic and thromboembolic complications in the study patients

Variable	ASA Group			Total	p Value
	None	Stopped	Continued		
Overall complications*	54 (4.9)	5 (4.6)	3 (2.4)	62 (4.6)	0.454
Complication category					
Hemorrhagic	7 (0.6)	1 (0.9)	1 (0.8)	9 (0.7)	0.921
Intracranial	7 (0.6)	0 (0)	1 (0.8)	8 (0.6)	
Extracranial	0 (0)	1 (0.9)	0 (0)	1 (0.1)	
Thromboembolic	15 (1.3)	2 (1.9)	1 (0.8)	18 (1.3)	0.779
Other	32 (2.9)	2 (1.9)	1 (0.8)	35 (2.6)	0.332
Hemorrhagic complications					
Intracerebral hematoma	5 (0.4)	0 (0)	1 (1)	6 (0.4)	NA
Epidural hematoma	2 (0.2)	0 (0)	0 (0)	2 (0.2)	NA
Hemorrhagic (extracranial)	0 (0)	1 (1)	0 (0)	1 (0.1)	NA
Thromboembolic complications					
Deep venous thrombosis	8 (0.7)	0 (0)	1 (1)	9 (0.7)	NA
Pulmonary embolism	7 (0.6)	1 (0.9)	0 (0)	8 (0.6)	NA
Stroke	0 (0)	1 (0.9)	0 (0)	1 (0.1)	NA

Data given as number and percentage of total (%) per operation unless otherwise indicated.

* Includes all complications related to surgery, i.e., hemorrhagic, thromboembolic, and others.

one can assume that if major bleeding events are reduced to the levels of non-ASA patients, the benefits of ASA continuation might be more apparent, particularly for those with high cardiovascular risk, as previously suggested by Lee et al.[23]

Current anesthesiology and cardiology guidelines recommend perioperative ASA continuation in patients with low to intermediate bleeding risk and high cardiovascular risk.[9,27] Intracranial surgeries, along with intramedullary spinal surgeries, are considered high-risk bleeding procedures and therefore are exempt from recommendations for ASA continuation, even in patients with high cardiovascular risk (e.g., secondary prevention patients).[27] However, we are aware of no solid data to justify these recommendations. It is well-known that neurosurgeons are concerned about intracranial hemorrhages due to potentially devastating results, and thus almost universally avoid perioperative antiplatelet continuation.[5,20] A national survey of neurosurgeons in Germany investigating ASA use before intracranial surgery showed that 77.5% of the respondents considered that patients taking low-dose ASA were at increased risk for excessive perioperative hemorrhage. Of the respondents, 58% reported personal experience with perioperative hemorrhage.[20] The same group also reported results of a survey for spinal surgery, which revealed similar percentages of perioperative hemorrhage. However, in this related study, only a small fraction (5%) of neurosurgeons would perform spinal surgeries under ASA medication.[21]

There are only a handful of published studies regarding the perioperative use of ASA in the neurosurgical literature. These are primarily focused on either emergency surgeries[6,10,17,18,23] or spinal procedures.[1,25,28] Two recent systematic reviews showed that there is no strong evidence demonstrating a difference in intraoperative blood loss, operation time, and postoperative complications between patients that continued or discontinued ASA who underwent spinal surgery.[8,16] Preinjury antiplatelet therapy also did not influence the rates of hemorrhagic complications and reoperation after decompressive craniectomy for traumatic brain injury.[17] Lee et al. showed that in patients aged ≥ 65 years undergoing emergency neurosurgery for traumatic intracranial hemorrhage, preoperative low-dose ASA treatment was not associated with increased perioperative bleeding, hospital length of stay, or in-hospital mortality.[23] Likewise, Kamenova et al. demonstrated comparable recurrence rates with and without discontinuation of low-dose ASA in patients undergoing burr-hole drainage for chronic subdural hematoma.[18] In a matched-pair analysis of ruptured aneurysms, Bruder et al.[6] showed that although ASA-treated patients (144 of 1422 patients with aneurysmal subarachnoid hemorrhage) more often had aneurysmal rebleeding (4.7% vs 2.3%, p = 0.3) and treatment-related hemorrhagic complications (13.9% vs 6.2%, p = 0.06), there were no differences in favorable outcome (modified Rankin Scale score 0–2) between the ASA and control groups (49.3% vs 52.1%, p = 0.7).

To the best of our knowledge, there are only two prior studies that reported perioperative ASA use in elective intracranial tumor surgery, with both having a small number of patients.[26,29] Their findings were similar to the present results. In their elective cranial tumor surgery cohort, Rahman et al.[29] detected no statistical differences between no-ASA (n = 368), discontinued-ASA (n = 55), and continued-ASA (n = 28) groups for outcomes including bleeding complications, need for reoperation, or thrombotic complications. Ogawa and Tominaga also found no difference in operation time, intraoperative bleeding, and length of stay between 15 patients on antithrombotic agents and 15 control patients undergoing transsphenoidal surgery for sellar and parasellar tumors.[26] The present study lends further support to the abovementioned works and demonstrates that acceptably low rates of hemorrhagic complications can

TABLE 5. Univariate/subgroup analyses of potential risk factors for hemorrhagic and thromboembolic complications irrespective of ASA status

Variable	n	Hemorrhagic Complications			Thromboembolic Complications		
		n (%)	95% CI	p Value	n (%)	95% CI	p Value
Age, yrs							
<65	948	5 (0.5)	0.2–1.2	0.463	12 (1.3)	0.7–2.2	0.795
≥65	398	4 (1.0)	0.3–2.6		6 (1.5)	0.6–3.3	
Sex							
Male	656	4 (0.6)	0.2–1.5	1.000	15 (2.3)	1.3–3.7	0.003
Female	690	5 (0.7)	0.2–1.6		3 (0.4)	0.1–1.3	
Tumor type							
Astrocytoma	350	3 (0.8)	0.2–2.5	0.703	3 (0.9)	0.2–2.5	0.588
Meningioma	331	2 (0.6)	0.1–2.2	1.000	7 (2.1)	0.9–4.3	0.170
Metastasis	199	1 (0.5)	0.01–2.8	1.000	1 (0.5)	0.01–2.8	0.500
Schwannoma	227	0 (0)	0.0–1.6	0.371	5 (2.2)	0.7–5.1	0.207
Other	239	3 (1.3)	0.3–3.6	0.219	2 (0.8)	0.1–3.0	0.457
Tumor grade							
Low/benign	825	4 (0.5)	0.1–1.2	0.298	15 (1.8)	1.0–2.3	0.053
High/malignant	521	5 (0.1)	0.3–2.2		3 (0.6)	0.1–1.7	
Tumor location							
Supratentorial	954	7 (0.7)	0.3–1.5	1.000	13 (1.4)	0.7–2.3	1.000
Infratentorial	392	2 (0.5)	0.1–1.8		5 (1.3)	0.4–2.9	
Deep	762	5 (0.6)	0.2–1.5	1.000	14 (1.8)	1.0–3.0	0.092
Superficial	584	4 (0.7)	0.2–1.7		4 (0.7)	0.2–1.7	
Intraaxial	763	8 (1.0)	0.4–2.0	0.087	6 (0.8)	0.3–1.7	0.055
Extraaxial	583	1 (0.2)	0.0–0.1		12 (2.0)	1.0–3.6	
EOR							
Complete	1045	7 (0.7)	0.3–1.4	1.000	13 (1.2)	0.7–2.1	0.579
Incomplete	301	2 (0.7)	0.1–2.4		5 (1.7)	0.5–3.9	

p values obtained using the chi-square test.

be achieved with a strict perioperative management protocol in patients where ASA continuation is deemed necessary due to their high cardiovascular risk. Furthermore, this study also found that male patients with deep-seated, extraaxial (skull base) tumors are at higher risk for developing thromboembolic complications, possibly due to prolonged operative time and hospitalization. Therefore, these patients may arguably benefit from ASA continuation even when their apparent cardiovascular risk is considered low.

The present study has several specific strengths. First, this study includes the largest elective intracranial tumor surgery cohort with and without perioperative ASA use that we are aware of to date. Both ASA groups (continued and discontinued) consist of more than 100 patients in each, enough to observe significant differences in terms of complications. These two groups were also similar in demographic and tumor characteristics, thus permitting a fair comparison. Furthermore, all patients underwent operations in a single center and by a single lead surgeon with experience in skull base and neurooncological surgery. Finally, the perioperative management protocols (antiplatelet discontinuation, hemostasis, blood pressure control, etc.) were uniform across the study period. To ensure accuracy and eliminate bias, data regarding the ASA status and com-

plications were double-checked and verified by two neurosurgeons who were not involved in the management of the patients and blinded to the study. The completeness of the data were satisfactory. Besides these strengths, the study also has certain limitations. First, as a retrospective study of a surgical series, it thus suffers from all inherent biases due to this design. Second, it does not involve randomization. Therefore, not all baseline characteristics were the same across all groups. And third, the overall complication rates were low, thus it is not sufficiently powered for the analysis of study subgroup differences. Therefore, a well-designed, large, multicenter, prospective randomized controlled trial is warranted to clarify actual risks and benefits of ASA continuation in high-risk patients undergoing elective craniotomy.

Conclusions

In this cohort, there was no clear evidence for an increased rate of hemorrhagic complications with perioperative ASA use in intracranial tumor surgery. Ischemic and thromboembolic events are similar between the no-, stopped-, and continued-ASA groups. This may reflect a relative risk reduction for the continued-ASA group, if the

baseline differences in thrombotic risk levels between the groups are considered. Therefore, in patients at high cardiovascular risk, ASA can be safely continued throughout the perioperative period for elective brain tumor surgery if potential benefits outweigh the risks of ASA continuation. Meticulous surgical technique and hemostasis combined with good perioperative care yield excellent results irrespective of a patient's ASA status. Taken together, this study challenges the belief that ASA should be discontinued before all elective intracranial surgeries. We believe that the present findings with this retrospective study provide a basis for future randomized clinical trials to establish actual risks and benefits of cranial surgery with respect to perioperative ASA status.

Acknowledgments

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Disclosures

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