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Is SSRI use a risk factor for intracranial hemorrhage after craniotomy for tumor resection?

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ABSTRACT

Introduction: Prior studies have identified SSRI use as a risk factor for certain adverse bleeding outcomes. However, the risk of significant bleeding from perioperative SSRI use after brain tumor resection remains largely undetermined. This study evaluates if patients taking SSRIs perioperatively have a higher risk of intracranial hemorrhage (ICH) following elective craniotomy for tumor resection.

Methods: Researchers reviewed electronic medical records of patients age 18 and older, who received elective craniotomy for tumor resection between 2010 and 2019. Data collection included subject demographics and relevant medical history. We compared intracranial hemorrhage rates and risks between perioperative SSRI-use cohorts.

Results: Of 1,061 patients, 796 (75%) did not use SSRIs perioperatively while 265 (25%) used SSRIs perioperatively. Among those using perioperative SSRIs, 8 patients (3.0%) experienced an ICH within 1 week and 11 patients (4.2%) had an ICH within 1 month. Similarly, for those who stopped SSRI use perioperatively, we found 31 patients (3.9%) experienced an ICH within 1 week and 40 patients (5.0%) had an ICH within 1 month. Using logistic regression analysis, the relative risk for perioperative SSRI-use and ICH was statistically non-significant at 0.692 (95% CI: 0.260 - 1.839, $p = 0.460$).

Conclusions: Based on our results, perioperative SSRI use does not appear to result in an increased risk of bleeding within 1 week or month of craniotomy for tumor resection. These results remained consistent when controlled for several additional bleeding comorbidities and demographics between cohorts

Introduction

Selective serotonin reuptake inhibitors (SSRIs) remain one of the most prescribed medications in the United States and often require a long-term prescription.[1] They are widely used in treating a variety of psychiatric illnesses such as major depressive disorder, panic disorder, and non-psychiatric conditions including neuropathic pain. SSRIs are commonly considered in treating comorbid psychiatric conditions in patients with brain tumors. A recent survey of Turkish neurosurgeons suggests roughly half of neurosurgeons may routinely prescribe antidepressants, with SSRIs and brain tumor specialists the most common drug class and specialty, respectively.[2]

Notably, many recent studies evaluating surgical outcomes have demonstrated associations of increased bleeding or need for transfusions with serotonergic antidepressant drug use.[3–7] These trends remained largely consistent across the multiple surgical specialties represented by those studies. Additional studies have highlighted the positive correlation between SSRI use and intracranial hemorrhage.[8–10] However, studies remain mixed regarding SSRI use and risk of stroke, with some studies concluding no association.[11–15] Yet documentation specifically suggests an increased risk of spontaneous intracerebral hematoma with SSRI use.[9] These studies largely support a need for further investigation between bleeding associated with SSRI use and neurosurgical procedures.

Regarding a likely mechanism of interaction, researchers believe these effects are secondary to serotonin transporter inhibition on platelet membranes.[16] These effects are unintentional under current drug indications, as the primary target of SSRIs are serotonin transporters located on neuronal cell membranes within the central nervous system. Because of these unanticipated effects, SSRI use is less likely to be a primary consideration when evaluating patient risk factors for surgery. The need for further study of adverse bleeding events associated with SSRIs are compounded by findings of synergistic effects with

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Abbreviations

CT	computed tomography
ICH	intracranial hemorrhage
MRI	magnetic resonance imaging
POH	Post operative intracranial hemorrhage
SSRI	selective serotonin reuptake inhibitor

traditional anticoagulants, such as warfarin.[10,14,17]

Lastly, despite their extensive use and effects on hemostasis, relatively few publications in the neurosurgical literature have explored the effects of SSRIs on craniotomies, specifically craniotomies for tumor resection. Many of the foundational association studies referenced prior have pooled together intracranial hemorrhage events, leaving evaluation of the more specific SSRI bleeding and tumor resection association largely unanswered. A very recent case-report has begun this evaluation by demonstrating SSRI use is associated with increased intratumoral hemorrhage from meningioma surgery.[18] To the best of our knowledge, this will be the first cohort study that aims to determine if there is an association between SSRI use and increased relative risk of intracranial bleeding after craniotomy for tumor resection.

Methods

A retrospective cohort study was performed at the University of Kansas Medical Center. Institutional Board Review approval was obtained (STUDY#00147417). Analysis of patient electronic medical records who received care at The University of Kansas Medical Center (KUMC) between January of 2010, and December of 2019 were obtained using the HERON identification system (CTSA Award #UL1TR002366). All patients were 18 years of age or older and underwent elective craniotomy for brain tumor resection. We compared rates of intracranial hemorrhage events (outcome) after craniotomy and tumor resection between patients taking SSRIs perioperatively (exposed) with those not taking SSRIs (non-exposed). For patients taking SSRI's perioperatively, the medication was continued in the perioperative period and day of surgery without interruption.

Additionally, we evaluated trends in demographic and clinical data including age, sex, use of antithrombotic agents, several comorbid conditions, and post-operative radiation therapy. Clinically significant findings were defined as any change in neurological status of the patient. Significant intracranial hemorrhage was defined as resulting in a new neurologic deficit or requiring evaluation for treatment intervention. Radiographic confirmation of intracranial hemorrhage (ICH) was made using post-operative imaging including computed tomography (CT) and magnetic resonance imaging (MRI) scans. Coagulation profile studies including PT, PTT, INR, Hemoglobin, Hematocrit, platelet count, and fibrinogen are obtained routinely.

Statistical analysis was performed using linear and logistic regression analyses. Results with a $p \leq 0.05$ were considered significant. Statistical analysis was performed using SPSS Version 27 (IBM Corp.). The primary outcome of interest was significant postoperative intracranial hemorrhage and SSRI use. The outcome variable of the regression model was intracranial hemorrhage within 1 month of procedure. Secondary endpoints were rates of bleeding revision surgery. The following patient variables in addition to SSRI use, tumor descriptors, and bleeding outcomes were included in the risk of significant hemorrhage model: age at time of surgery-numerical; sex-binary (history of): hypertension-binary; hyperlipidemia-binary; diabetes mellitus-binary; heart failure-binary; coronary artery disease-binary; peripheral vascular disease-binary; stroke-binary; alcohol use disorder-binary; smoking-binary. Regression analysis was multivariate with significant hemorrhage within 1 month as the primary outcome event of interest. Input variables included SSRI use, tumor characteristics, and demographic variables listed above. The variable "death within one month" was used as a predictor variable in the model as an indirect representation of patients with clinical concern for limited life expectancy as an outcome of surgery.

Results

The cohort consisted of 1061 patients, including 265 and 796 SSRI and non-SSRI users, respectively. Of these, 492 (46%) patients were male, and the median age of participants was 52 with a range of 18–89. The median age at surgery was 52 years old. Tumor pathologies present included 267 meningiomas, 366 gliomas, 219 metastases, and 209 other histopathology (DNET, hemangioblastoma, cavernoma, etc.).

Of 1061 patients, 796 (75%) did not use SSRIs perioperatively while 265 (25%) used SSRIs perioperatively. Among those using perioperative SSRIs, 8 patients (3.0%) experienced an ICH within 1 week and 11 patients (4.2%) had an ICH within 1 month. Similarly, for those who stopped SSRI use perioperatively, we found 31 patients (3.9%) experienced an ICH within 1 week and 40 patients (5.0%) had an ICH within 1 month. Using logistic regression analysis, the relative risk for perioperative SSRI-use and ICH was found to be statistically non-significant at .692 (95% CI: .260–1.839, $p = 0.460$). Other measured variables did not differ significantly between cohorts.

Among patients experiencing significant intracranial hemorrhage, the need for further surgical intervention was observed. Of the 8 SSRI patients with ICH at 1 week, 4 (50%) required another surgery due to the bleeding. Regarding the 31 non-SSRI patients with ICH at 1 week, 10 (32%) required reoperation. Within 1 month, 5 (45%) SSRI using, and 14 (35%) non-SSRI using patients required reoperation perioperatively. The confounding variables of anticoagulant or antiplatelet use were factored into the multivariate logistic regression for calculating the risk of bleeding within one month after surgery. The authors did not specifically calculate the bleeding risk for this subgroup due to the known effects of increased bleeding risk.

Discussion

Craniotomy with tumor excision is a common and essential surgery for the multifaceted treatment of patients with a primary or metastatic CNS neoplasm. However, post-operative ICH is a well-known complication and an important cause of postoperative morbidity and mortality. Several well-established risk factors can contribute to the formation of a postoperative ICH including tumoral characteristics, intraoperative and preoperative factors. Among the latter are factors such as older age, hypertension, primary and iatrogenic mediated hematological and coagulation dyscrasias. In order to reduce the risk of postoperative ICH (POH), preventive measures are usually initiated in the preoperative setting and include the cessation of antiplatelet, anticoagulation therapies and other medication with established potent antithrombotic effects.

Recent studies have shown that SSRI use is associated with an increased risk of spontaneous ICH secondary to its antiplatelet effect, particularly in the first month of initiation. The effect has been shown to become even more pronounced when used concurrently with an anticoagulant therapy.[8] Other studies analyzing the effect of SSRIs and intracranial hemorrhage generally, after stroke, or in conjunction with thrombolytic therapy have concluded no significant increased risk of hemorrhage.[19–21] However, studies have not yet assessed the perioperative use of SSRIs on the development of POH after craniotomy for tumor resection.

This analysis is the first to look at the association between SSRIs and the development of ICH after elective cranial tumor surgery. In this cohort, perioperative SSRI use was not found to be an independent risk for developing acute ICH after tumor resection ($p = 0.657$). This data supports the safe and continued use of SSRI medications for treating patients' comorbid psychiatric conditions during the perioperative

period. However, the context of this recommendation should be made while acknowledging the relatively large confidence interval surrounding the relative risk of ICH after perioperative SSRI use. Despite the significant data set of patients evaluated, the rarity of significant postoperative bleeding events led to a relative paucity of event data and larger than anticipated statistical intervals.

These results presented in this study remain consistent when controlled for several additional bleeding comorbidities and demographics between cohorts. This is further supported by the similarity between cohorts seen in (Table 1). All patients included in this data set were treated at a single large academic medical center. Additionally, most patients treated at this institution reside in the Midwestern United States. With that in mind, the results presented in this study may better reflect outcomes of this geographic population.

Based upon our analysis, patients who were continued on perioperative SSRI medications appear to have no increased risk of experiencing intracranial hemorrhage within 1 week or month of craniotomy for tumor resection, as shown in (Tables 2 and 3). There were additional statistically significant trends uncovered during logistic regression analysis. Protective variables included female gender. Conversely, harmful variables included diabetes mellitus, and death within 6 months of surgery (see Table 4). It currently remains unclear why female gender may confer protective effects and remains an opportunity for future research. Notably, the histological class of tumor had no significant effect of postoperative ICH risk in these cohorts.

Lastly, our study is not without limitations. Only 25% of patients in this sample were continued on perioperative SSRI medications. However, our understanding is that the sample size was statistically adequate to accurately compare both exposure cohorts without excessive bias from unbalanced confounding factor representation. The primary limitations of this study design include the inherent potential bias of retrospective data collection. Furthermore, known risk factors such as older age and hypertension did not contribute significantly to the risk of bleeding in our regression model despite a large sample size which should have adequately powered such effects. Although not the focus of this analysis, the absence of these effects should serve to limit the certainty placed upon the results of this bleeding risk model.

Future research efforts should attempt to reduce the statistical uncertainty by conducting larger studies of patients undergoing neurosurgical procedures, as well as research that evaluates other commonly used medications (e.g., opioids, benzodiazepines) with regards to their potential relationship to postoperative intracranial hemorrhage. Clinicians should also be cognizant of the potential risks associated with stopping medication therapy abruptly, particularly in patients with severe comorbid conditions or using short-acting SSRI medications. This remains a particularly important consideration as SSRIs can be a useful adjunct in the perioperative management of patients with brain tumors

Table 1
Demographics, comorbidities, and tumor pathologies of study participants.

	Perioperative SSRI Users	Non-perioperative SSRI Users	Statistical Significance. Chi-Square, t-Test
Demographics			
Total Patients	265	796	
Sex: Female	168 (63%)	401 (50%)	**0.000**
Median Age (range)	56 (18–83)	51 (18–89)	0.811
Comorbidities			
Hypertension	124 (47%)	324 (41%)	0.096
Hyperlipidemia	81 (31%)	223 (28%)	0.473
Diabetes Mellitus	39 (15%)	95 (12%)	0.283
Heart Failure	25 (9%)	57 (7%)	0.286
Coronary Artery Disease	17 (6%)	50 (6%)	0.938
Peripheral Vascular Disease	19 (7%)	48 (6%)	0.607
Prior Stroke	14 (5%)	32 (4%)	0.484
Alcohol Use Disorder	4 (2%)	10 (1%)	0.998
History of Smoking	123 (46%)	367 (46%)	0.987
Chronic Anticoagulant Use	31 (12%)	74 (9%)	0.310
Chronic Antiplatelet Use	90 (34%)	212 (27%)	**0.027**
Tumor & Characteristics			
Meningioma	65 (25%)	202 (25%)	
Glioma	81 (31%)	285 (36%)	
Other	119 (44%)	309 (39%)	
Overall Pathology Distribution			0.307
Supratentorial Location	206 (78%)	637 (80%)	0.477
Gross Total Resection Achieved	172 (65%)	472 (59%)	0.112
Deficit resolution within 6 months	5 (33%)	28 (63%)	0.082

Table 2
Intracranial hemorrhage rates between perioperative SSRI users and non-users.

	Perioperative SSRI	Non-perioperative SSRI	Statistical Significance. Chi-Square, t-Test
1 week ICH			
Total ICH (% patients)	8 (3.0%)	31 (3.9%)	0.650
Symptomatic	6 (75%)	26 (84%)	0.947
Required Surgery	4 (50%)	10 (32%)	0.604
Radiographic only	2 (25%)	5 (16%)	0.999
1 month ICH			
Total ICH (% patients)	11 (4.2%)	40 (5.0%)	0.508
Symptomatic	8 (73%)	35 (88%)	0.468
Required Surgery	5 (45%)	14 (35%)	0.777
Radiographic only	3 (27%)	5 (13%)	0.411

Table 3
Bleeding risk based upon multivariate regression analysis of perioperative SSRI use, tumor pathology, and outcome.

Variable	Relative Risk	95% CI	Significance
Perioperative SSRI use	**.692**	**0.260–1.839**	**0.460**
Any tumor type	1.013	0.892–1.151	0.840
Glioma	1.002	0.409–2.454	0.997
Metastasis	1.889	0.771–4.630	0.164
Other	2.070	0.678–6.322	0.202
Death within 6 months	**3.926**	**1.944–7.930**	**0.000**

Table 4
ICH risk based upon demographics and comorbidities compared with multivariate logistic regression.

Variable	Relative Risk	95% CI	Significance
Sex: Female	**0.487**	**0.271–0.877**	**0.017**
Age at Surgery	1.014	0.994–1.034	0.176
Hypertension	1.066	0.556–2.043	0.848
Hyperlipidemia	0.796	0.396–1.601	0.522
Diabetes Mellitus	**2.569**	**1.211–5.448**	**0.014**
Heart Failure	0.678	0.202–2.282	0.531
Coronary Artery Disease	0.893	0.259–3.073	0.857
Peripheral Vascular Disease	0.581	0.178–1.896	0.369
Stroke	1.159	0.350–3.842	0.809
Alcohol Use Disorder	0.703	0.071–6.951	0.763
Smoking History	0.740	0.415–1.320	0.308

due to the high prevalence of depression and anxiety from both the diagnosis of a brain tumor as well as the disruption of normal neural networks.[22]

Conclusions

Based on our results, observed in patients from the Midwest United States, perioperative SSRI use does not appear to result in an increased risk of bleeding within 1 week or month of craniotomy for tumor resection. These results remained consistent when controlled for several additional bleeding comorbidities and demographics between cohorts. Lastly, the primary limitations of this study include the potential bias of retrospective data collection.

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Preliminary presentation

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CRediT authorship contribution statement

Bradley J. Estes: Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Ahmad R. Masri:** Writing – review & editing, Validation, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Roukoz Chamoun:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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