Serotonergic Antidepressants and Risk for Traumatic Intracranial Bleeding

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Background: Serotonergic antidepressants may predispose to bleeding but the effect on traumatic intracranial bleeding is unknown.

Methods: The rate of intracranial bleeding in patients with antidepressant medication was compared to patients not antidepressants in a cohort of patients with acute head injury. This association was examined by using a consecutive cohort of head trauma patients from a Finnish tertiary center emergency department (Tampere University Hospital, Tampere, Finland). All consecutive (2010–2012) adult patients (n = 2,890; median age = 58; male = 56%, CT-positive = 22%, antithrombotic medication users = 25%, antidepressant users = 10%) who underwent head CT due to head trauma in the emergency department were included.

Results: Male gender, GCS < 15, older age, and anticoagulation were associated with an increased risk for traumatic intracranial bleeding. There were 17.8% of patients not taking antidepressants and 18.3% of patients an antidepressant who had traumatic intracranial bleeding (p = 0.830). Among patients who were taking antithrombotic medication, 16.6% of the patients not taking antidepressant medication, and 22.5% of the patients taking antidepressant medication, had bleeding (p = 0.239). In a regression analysis, traumatic intracranial hemorrhage was not associated with antidepressant use.

Conclusions: Serotonergic antidepressant use was not associated with an increased risk of traumatic intracranial hemorrhage.

Keywords: brain injuries, traumatic, intracranial hemorrhages, antidepressant agents, anticoagulation, antithrombotic agents (MeSH)
INTRODUCTION

Intracranial bleeding is the most severe and feared complication of head trauma. Hemorrhagic lesions may be life-threatening, require urgent neurological care, and they might cause long-term disability. Several risk factors for intracranial bleeding following head trauma include age, high-energy trauma mechanism, fall from a height, history of coagulopathy, and use of anticoagulants (1–5).

Antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), are a commonly used group of medications. The prevalence of antidepressant use has been estimated to be between 2.7 and 15.7% in the adult population in the European Union and United States (6, 7). There is a concern that SSRIs have been linked to increased risk of bleeding, including hemorrhagic stroke (8–18). This increase in bleeding risk is thought to be due to the role of serotonin in platelet aggregation, which is inhibited by SSRIs, as well as to a direct decrease in platelet adhesion to both collagen and fibrinogen (9, 19–21)—important processes in the initiation of hemostasis.

The possible association between SSRI use and risk for intracranial bleeding is not well-understood. Theoretically, small subcortical microbleeds following shearing forces (acceleration/deceleration) to the brain might enlarge in the setting of compromised platelet function associated with use of SSRIs. The objective of this study was to investigate the risk for intracranial hemorrhage in patients on serotonergic antidepressant therapy who present to the emergency department with head trauma and undergo computed tomography (CT). We hypothesized that the use of serotonergic antidepressants would be associated with an increased risk for intracranial hemorrhages following head injury.

MATERIALS AND METHODS

Study Setting and Ethics

The current study included patients initially enrolled in the Tampere Traumatic Head and Brain Injury Study (study code: NCT01427959). All patients were from the ED of the Tampere University Hospital (Tampere, Finland). The ED provides health services for a joint municipal authority of 22 municipalities (both urban and rural) with a total of approximately 470,000 residents. The Tampere University Hospital is the main trauma center and only neurosurgical referral hospital in the hospital district. In this study, the minimum criteria for traumatic brain injury (TBI) were defined as follows: either blunt injury to the head or acceleration/deceleration type injury resulting in an initial Glasgow coma scale (GCS) score of 13–15, witnessed loss of consciousness, disorientation, or amnesia. These criteria were used to include patients with a TBI and to exclude patients with an isolated head injury without signs of TBI. The endpoint of the study was acute intracranial traumatic hemorrhage visible on the primary CT scan.

This study was approved by the Ethics Committee of Pirkanmaa Hospital District, Tampere, Finland (identifier: R10027). Institutional ethics and research board approval was also obtained.

Study Sample

The participants were enrolled during a 2-year period between August 2010 and July 2012. The patients in this cohort consisted of all consecutive patients who underwent head CT due to acute head trauma (n = 3,023). A detailed retrospective data collection was conducted on demographics, injury-related data, premorbidity health, medication, clinical characteristics, and neuroimaging findings. In this retrospective sample, referral criteria for acute head CT were based on the Scandinavian Guidelines for Initial Management of Minimal, Mild, and Moderate Head Injuries from 2000 (22). The data collection has been described in detail in previous publications (23, 24). For the present study, patients under 16 years (n = 133) were excluded and in total 2,890 adult patients were included.

Medication Data

Antidepressants that were considered serotonergic and in use in Finland were: (i) citalopram, (ii) escitalopram, (iii) sertraline, (iv) fluoxetine, (v) paroxetine, (vi) venlafaxine, (vii) duloxetine, (viii) vortioxetine, (ix) amitriptyline, (x) doxepin, and (xi) trimipramine. Drugs were further grouped into SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) based on their structure and pharmacodynamic properties.

Information on the current use of serotonergic antidepressants was collected from the hospital records. Antithrombotic medication use was also recorded. Antiplatelet medications included acetylsalicylic acid (ASA), ASA-dipyridamole, dipyridamole, ticlodipine, clopidogrel, prasugrel, and ticagrelor. Anticoagulant medication included warfarin, apixaban, dabigatran, edoxaban, and rivaroxaban, and low-molecular weight heparins (LMWH).

Imaging

All of the head CT scans were interpreted by a board certified neuroradiologist and systematically coded using an independent coding protocol (24). The cohort was collected before the Common Data Elements (CDEs) for TBI imaging by the National Institute of Neurological Disorders and Stroke were established (25). However, all CDEs possible with non-contrast structural CT scan were included in the neuroradiological case report form. The focus of this study was on hemorrhagic head CT lesions (epidural hematoma, subdural hematoma, subarachnoid hemorrhage, contusion, intracerebral hemorrhage, and intraventricular hemorrhage).

Statistical Analysis

Dichotomous variables were compared using the chi-square test for proportions and continuous variables using the Mann-Whitney U-test. Interactions between antithrombotic use and antidepressant use were analyzed with two-way ANOVA. Unconditional logistic regression modeling was performed to estimate the odds ratios (ORs) and 95% CIs of acute intracranial hemorrhage in patients on serotonergic antidepressants while controlling for multiple possible confounders (GCS, antiplatelet medication, anticoagulation, gender, and age). The regression model confounders were selected based on their clinical relevance.
## TABLE 1 | Characteristics of the study sample.

| Variable                          | All CT-scanned patients \( n = 2,890 \) | CT-scanned patients on serotonergic antidepressants \( n = 287 \) | CT-scanned patients without serotonergic antidepressants \( n = 2,603 \) | \( p \)-Value |
|-----------------------------------|----------------------------------------|-------------------------------------------------|-------------------------------------------------|---------------|
| Age (years)                      | Md = 58.4 Range = 16.0–103.8           | Md = 68.7 Range = 16.4–94.6                      | Md = 57.4 Range = 16.0–103.8                    | <0.001        |
|                                   | \( n \) \%                             | \( n \) \%                                       | \( n \) \%                                       |               |
| Men                               | 1,619 56.0                              | 179 62.3                                        | 1,092 42.0                                      | <0.001        |
| Women                             | 1,271 44.0                              | 108 37.6                                        | 1,511 58.0                                      | <0.001        |
| Diseases of the circulatory system | 1,542 53.4                              | 122 42.5                                        | 1,420 54.6                                      | <0.001        |
| Mental and behavioral disorders   | 774 26.8                                | 154 53.7                                        | 620 23.8                                        | <0.001        |
| Diseases of the nervous system    | 711 24.6                                | 120 41.8                                        | 591 22.7                                        | <0.001        |
| Injury mechanism                  |                                        |                                                |                                                |               |
| Unknown                           | 72 2.5                                  | 6 2.1                                           | 66 2.5                                          | 0.646         |
| Car accident                      | 286 9.9                                 | 11 3.8                                          | 275 10.6                                        | <0.001        |
| Ground-level fall                 | 1,563 54.1                              | 218 76.0                                        | 1,345 51.7                                      | <0.001        |
| Motorcycle accident               | 49 1.7                                  | 2 0.7                                           | 47 1.8                                          | 0.167         |
| Bicycle accident                  | 116 4.0                                 | 7 2.4                                           | 109 4.2                                         | 0.152         |
| Fall from a height                | 301 10.4                                | 21 7.3                                          | 280 10.8                                        | 0.070         |
| Sports                            | 54 1.9                                  | 1 0.3                                           | 53 2.0                                          | 0.045         |
| Violence                          | 218 7.5                                 | 12 4.2                                          | 206 7.9                                         | 0.023         |
| Other, not specified              | 175 6.1                                 | 9 3.1                                           | 166 6.4                                         | 0.029         |
| Any antithrombotic medication     | 710 24.6                                | 121 42.2                                        | 589 22.6                                        | <0.001        |
| Anticoagulant medication          |                                        |                                                |                                                |               |
| Warfarin                          | 329 11.4                                | 40 13.9                                         | 290 11.1                                        | 0.157         |
| Apixaban                          | 0 0                                    | 0 0                                             | 0 0                                             | N/A           |
| Dabigatran                        | 1 0.0                                  | 0 0                                             | 1 0                                             | 0.740         |
| Rivaroxaban                       | 0 0                                    | 0 0                                             | 0 0                                             | N/A           |
| Low molecular weight heparin      | 21 0.7                                 | 2 0.7                                           | 19 0.7                                          | 0.951         |
| Antiplatelet medication           |                                        |                                                |                                                |               |
| Acetylsalicylic acid              | 329 11.4                                | 74 25.8                                         | 255 9.8                                         | <0.001        |
| Acetylsalicylic acid-dipyridamol  | 47 1.6                                  | 8 2.8                                           | 39 1.5                                          | 0.101         |
| Clopidogrel                       | 24 0.8                                  | 4 1.4                                           | 20 0.8                                          | 0.268         |
| Ticagrelor                        | 0 0                                    | 0 0                                             | 0 0                                             | N/A           |
| Acetylsalicylic acid and clopidogrel | 9 0.3                              | 1 0.3                                           | 8 0.3                                           | 0.906         |
| Dipyridamole                      | 8 0.3                                  | 0 0                                             | 8 0.3                                           | 0.347         |
| Glasgow coma scale score 15       | 1,509 52.2                              | 146 51.2                                        | 1,363 52.4                                      | 0.102         |
| Glasgow coma scale score 13–14    | 130 4.4                                 | 7 2.4                                           | 123 4.7                                         | 0.142         |
| Glasgow coma scale score 3–12     | 244 8.4                                 | 19 6.6                                          | 225 8.6                                         | 0.434         |
| Loss of consciousness, witnessed | 549 19.0                                | 30 10.5                                         | 519 19.9                                        | <0.001        |
| Post-traumatic amnesia            | 646 22.4                                | 55 19.2                                         | 591 22.7                                        | 0.172         |

CT, computed tomography; GCS was categorized as above in order to form subgroups of similar size.
TABLE 2 | Types of traumatic head CT lesions.

| Type of traumatic lesion | Total sample n = 2,890 | On antidepressant n = 287 | No antidepressant n = 2,603 | p-Value |
|--------------------------|------------------------|--------------------------|-----------------------------|---------|
| Skull fracture           | 157 (5.4)              | 11 (3.8)                 | 146 (5.6)                   | 0.208   |
| Epidural hematoma        | 19 (0.7)               | 1 (0.3)                  | 18 (0.7)                    | 0.495   |
| Subdural hematoma        |                        |                          |                             |         |
| Subdural hematoma, acute | 350 (12.1)             | 35 (12.2)                | 350 (13.4)                  | 0.963   |
| Subdural hematoma, chronic| 100 (3.5)              | 9 (3.1)                  | 91 (3.5)                    | 0.751   |
| Subdural hematoma, mixed density | 11 (0.4) | 1 (0.3)                  | 10 (0.4)                    | 0.926   |
| Traumatic subarachnoid hemorrhage | 278 (9.6) | 21 (7.3)                  | 257 (9.9)                   | 0.163   |
| Contusion                | 216 (7.5)              | 25 (8.7)                 | 191 (7.3)                   | 0.401   |
| Intraventricular hemorrhage | 85 (2.9)           | 7 (2.4)                  | 78 (3.0)                    | 0.596   |
| Microhemorrhage (diffuse axonal injury) | 11 (0.4) | 0 (0.0)                  | 11 (0.4)                    | 0.270   |
| Patients with any intracranial hemorrhagic lesion | 527 (18.2) | 51 (17.8)                 | 476 (18.3)                  | 0.830   |
| Acute traumatic lesion on head CT | 633 (21.9) | 53 (18.5)                 | 580 (22.2)                  | 0.138   |
| Acute hemorrhagic lesion on head CT (no CSDH) | 503 (17.4) | 47 (16.4)                 | 456 (17.5)                  | 0.628   |

CT, computed tomography; CSDH, chronic subdural hematoma.

RESULTS

The characteristics of the study patients are presented in Table 1. The median age of the patients was 58.4 years. The most common injury mechanism was a ground-level fall. Antithrombotic medication was used by 24.6%. The most common anticoagulant was warfarin, and the most used antiplatelet medication was ASA. The traumatic lesions are reported in Table 2. The most common hemorrhagic lesion was subdural hematoma. There were 17.8% of patients not taking antidepressants and 18.3% of patients on an antidepressant who had traumatic intracranial bleeding (p = 0.830). Among patients who were taking antithrombotic medication, 16.6% of the patients not taking antidepressant medication, and 22.5% of the patients taking antidepressant medication, had bleeding (p = 0.239).

The use of serotonergic antidepressants is presented in Table 3. Selective serotonin reuptake inhibitors were the most commonly used antidepressants (7.2%). Among antidepressant using patients the most common agents were citalopram (30.0%) and escitalopram (25.8%).

The logistic regression analysis was calculated for SSRI medication, SNRI medication, TCA medication, and any serotonergic antidepressant. Only acute traumatic hemorrhagic lesions were included and chronic subdural hemorrhages were excluded. The results are shown in Table 4.

Interactions between antithrombotic use and antidepressant use were analyzed with the two-way ANOVA. There was a statistically significant interaction with antiplatelet medication use and serotonergic antidepressant use (p = 0.006) but not with anticoagulant use and serotonergic antidepressant use (p = 0.590). Antiplatelet medication use was more common among patients taking serotonergic antidepressant medication (28.6 vs. 12.0%, p < 0.001).

In the univariate analysis, male gender, GCS under 15, older age, and anticoagulation were associated with an increased risk for an acute traumatic intracranial bleed. In the multivariate analyses, anticoagulation was not significantly associated with increased risk for bleeding. The number of patients was 1,883.
in the multivariate analyses due to missing GCS data. In the multivariate analysis with the SSRI medication, the ORs for traumatic intracranial hemorrhage were non-significant with SSRI, SNRI, and TCA medication, and also with any serotonergic antidepressant.

**DISCUSSION**

There is minimal literature on the association between serotonergic antidepressant use and intracranial bleeding risk after head trauma. The rate of traumatic hemorrhagic lesions was similar in patients taking antidepressant medication vs. those not taking antidepressants. The risk for traumatic intracranial hemorrhage did not increase in those taking antidepressants, compared to those who were not, even when there was concomitant use of antithrombotic medication. These results are important given the high incidence of head injuries, the widespread use of serotonergic antidepressants medications, and the prior reports of serotonergic antidepressant-related systemic bleeding complications.

To our knowledge, the only study that has partly assessed the effects of antidepressant and traumatic intracranial bleeding has been conducted by Ibañez Pérez De La Blanca et al. (27). In that study, 504 older patients (≥60 years) with mild TBI were examined. Risk factors for traumatic intracranial lesions were analyzed with a multivariate logistic regression model. In that model, SSRIs were combined with benzodiazepines. Ibañez Pérez De La Blanca et al. concluded that SSRIs and/or benzodiazepines were protective for CT-positive intracranial lesions (OR = 1.681, 95% CI = 1.042–2.714, p = 0.033). The authors suggested that these drugs could possibly serve as neuroprotectors in elderly patients.

The use of antidepressants has increased over the years and is especially prevalent among the elderly (6). Moreover, TBI in the elderly is a growing public health concern (28). Advancing age (24) and antithrombotic agents (29, 30) are generally acknowledged risk factors for intracranial hemorrhage, both spontaneous and traumatic. From a pharmacological perspective, serotonergic medication could increase the likelihood of traumatic intracranial bleeding (9). The baseline risk of TBI-related intracranial bleeding that is associated with medications should be greatest among elderly patients on antithrombotic medication. Intuitively, the possible incremental bleeding risk associated with serotonergic antidepressants would manifest in elderly patients who use blood thinners. Based on the findings from the literature on spontaneous intracranial hemorrhage, the bleeding risk should be greatest among the patients using the antidepressants with the highest degree of serotonin reuptake inhibition (e.g., paroxetine, duloxetine, sertraline, escitalopram, fluoxetine) (31).

Inconsistent with our primary study hypothesis, serotonergic antidepressants were not associated with increased risk for traumatic intracranial bleeding. This null finding was consistent throughout our study as we analyzed different subgroups. In line with the literature, age was a risk factor for CT-positive traumatic intracranial hemorrhage in the combined sample. However, contrary to the general assumption, antiplatelet medication use did not increase the risk for traumatic intracranial bleeding in our study. It is worth noting that ASA is prescription-free in Finland, and some cases of usage of this medication are not recorded in the medical records. Thus, some ASA medication usage might not have been detected by the researchers. It is well-known that the adherence to long-term medication is often poor, as the adherence rates average around 50% (32) and Finland is not an exception in this matter (33).

An interaction was found between antiplatelet medication and antidepressant use. Almost one third (28.6%) of the patients taking serotonergic antidepressant were also on antiplatelet medication. Even with this interaction, the incidence of intracranial bleeds was lower in antidepressant group, suggesting that this interaction did not affect the risk for intracranial bleeding.
Older patients have a high prevalence of heart and cardiovascular disease, and thus antithrombotic agents are more frequently used in this subgroup to reduce the risk or to prevent the onset of thromboembolic events. Older age increases independently the risk of major hemorrhage, particularly intracranial hemorrhage, in patients with atrial fibrillation, whether or not they are taking warfarin (34). Age is strongly correlated with brain atrophy which may independently increase the risk for traumatic ICH, whether or not the patient is on an antithrombotic (35). It is possible that the effect of age itself confounds the effects of antithrombotic agents in our study.

Our current findings have clinical implications in relation to the acute management of patients with head injuries. In the emergency assessment of these patients, the risk of intracranial hemorrhagic complications is a paramount consideration. Age, preexisting diseases, medication, and injury characteristics influence the risk of hemorrhage. Decision-making on initial emergency head CT scanning, need for in-hospital monitoring, stratification for monitoring strategies, administration of prothrombotic agents to correct coagulation, and necessity of repeated head CT imaging is largely based on the presumed overall risk of traumatic intracranial hemorrhagic complications.

Deciding who should undergo head CT scanning after a head trauma is one of the most debated questions in emergency medicine, especially for those with clinical signs of mild TBI. In clinical practice, patients sustaining a mild TBI while on anticoagulation or on antiplatelet drugs are frequently automatically deemed to be at high risk of intracranial bleeding. The majority of international guidelines on the management of acute head injury do not advise specifically on the care of patients who are anticoagulated mainly due to the lack of sufficiently powered studies to address management in such subpopulations (1, 36). The National Institute of Clinical Excellence (NICE), National Emergency X-Radiology Utilization Study (NEXUS II), CT in Head Injury Patients (CHIP), American College of Emergency Physicians (ACEP), and the European Federation of Neurological Societies (EFNS) recommendations advocate that all patients taking warfarin should have an immediate CT scan irrespective of injury severity, GCS, or neurological symptoms (1, 3, 37–39). In this study, the risk of intracranial bleeding for those on anticoagulation was small and non-significant after adjustment for other factors. Additionally, serotonergic antidepressants did not increase the risk of traumatic intracranial hemorrhage irrespective of antiplatelets and anticoagulants. Our findings emphasize the importance and usefulness of other variables, such as the GCS and age, in the assessment and imaging triage of patients with head injuries.

This study has several strengths. The study sample is large, and the medication and CT imaging data is comprehensive. The study includes the whole severity spectrum of TBI from head injuries with no signs of TBI to severe TBI. Also, adult patients from all age groups in varying health conditions were included, although importantly our samples include a large percentage of older adults. The medication use of each patient was reviewed thoroughly. All CT findings, including hemorrhagic and other traumatic lesions were systematically coded. The cohort represents an unselected sample of patients with head injury who were consecutively treated in one ED. Other than requiring a clinically indicated head CT scan of the head, no eligibility criteria were applied, making the study findings more generalizable. All of the patients were treated in the same ED and the CT scans were interpreted by neuroradiologists.

There are also limitations in this study. First, the data were collected retrospectively from hospital records and hence some relevant information was missing. This may have biased our estimation of the relationship between patient and injury characteristics, and head CT findings. Second, we were unable to collect data on the exact dosage of the antidepressant medication. As noted above, there is some uncertainty on the use of ASA because this drug is prescription-free in Finland. Third, there were few users of direct oral anticoagulants because their use was uncommon during the period when most of the data were collected. Fourth, mechanism of injury is important in emergency medicine as part of clinical decision making regarding whether to order a head CT. We did not include mechanism of injury in our regression model because we could not, with reasonable confidence, differentiate high energy mechanisms (vs. medium or low), and some mechanisms had very small sample sizes and a sizeable minority were unknown. Finally, we do not have sufficient data (e.g., findings of repeat head CT imaging) on the radiological progression of the hemorrhagic lesions.

Future high-level observational studies (including antidepressant dosage) such as prospective cohort studies might allow better estimation of the potential risk of SSRI use and traumatic intracranial hemorrhage. The results of this study suggest that the use of serotonergic antidepressants by patients with head injuries does not warrant special precautions in the initial ED assessment.

CONCLUSIONS

The use of serotonergic antidepressants was not associated with increased risk of intracranial hemorrhage after acute head trauma.

DATA AVAILABILITY STATEMENT

The statistical analyses and underlying data supporting the conclusions of this article will be made available by the authors to qualified researchers for research purposes, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Pirkanmaa Hospital District, Tampere, Finland (identifier: R10027). Written informed consent
from the participants’ legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HI wrote the statistical analysis plan, cleaned and analyzed the data, and drafted and revised the paper. GI, JP, JR, and JO contributed to drafting and revising the paper. AB and AK collected the imaging data and contributed to drafting and revising the paper. TL wrote the statistical analysis plan, monitored data collection for the study, and contributed to drafting and revising the paper. All of the authors have approved the final version.

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