Review Article

Risk of Intracranial Hemorrhage and Utilization of Selective Serotonin Reuptake Inhibitors: A Systematic Review and Meta-analysis

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Abstract

Background: Selective serotonin reuptake inhibitors (SSRIs) have the potential to reason an obtained hemostatic defect related to their capacity to inhibit platelet characteristics. Especially, SSRIs inhibit the serotonin transporter on platelets, causing a lower in intra platelet serotonin and diminished remarks activation at some point of dense granule secretion, leading to intracranial hemorrhage (ICH). **Aim:** This work aims to determine the safety of utilization of Selective Serotonin Re-uptake Inhibitors (SSRI), regarding the incidence of Intra-cranial hemorrhage (ICH). **Materials and Methods:** A systematic search was performed over different medical databases to identify Neurology studies, which studied the outcome of the SSRI users group versus the Non-SSRI users' group of patients. Using the meta-analysis process, either with fixed or random-effects models, we conducted a meta-analysis on the incidence of intracranial hemorrhage as the main primary outcome. **Results:** Seven studies were identified involving 153323 patients, with 19010 patients in the SSRI users group, and 134313 patients in the Non-SSRI users' group. The meta-analysis process revealed a significant increase in the incidence of intracranial hemorrhage in the SSRI users group compared to the Non-SSRI users' group (p=0.033). **Conclusion:** To conclude, SSRIs exposure after ICH is associated with both improvement in depressive symptoms and increased risk of recurrent hemorrhagic stroke. Clinical history, neuroimaging data, and genetic biomarkers may help to identify survivors of ICH more likely to safely tolerate SSRI use.

Keywords: Intracranial Hemorrhage; Selective Serotonin Reuptake Inhibitors (SSRI)

Introduction

The acute presentation of intracranial hemorrhage ICH can be difficult to differentiate from ischemic stroke. Signs and symptoms may additionally consist of headache, nausea, seizures, and focal or generalized neurologic signs. Findings which include coma, headache, vomiting, seizures, and neck stiffness, and raised diastolic blood strain growth the chance of ICH compared to ischemic stroke, but only neuroimaging can provide a definitive prognosis. Primary ICH is commonly a manifestation of underlying small vessel disease. First, longstanding high blood pressure results in hypertensive vasculopathy causing microscopic degenerative adjustments within the partitions of small-to-medium penetrating vessels, which is called lipohyalinosis. CAA is characterized by the deposition of amyloid-beta peptide (Aβ) inside the partitions of small leptomeningeal and cortical vessels. Although the underlying mechanism leading to the accumulation of amyloid remains unknown, the very last outcomes are degenerative adjustments inside the vessel wall characterized by the lack of smooth muscle cells, wall thickening, luminal narrowing, microaneurysm formation, and microhemorrhages. [1]

Selective serotonin reuptake inhibitors (SSRIs) are commonly encountered inside the perioperative period because they are widely used to deal with some fairly ordinary sicknesses, inclusive of depression, anxiety, panic sickness, obsessive-compulsive sickness, bulimia nervosa, and neuropathic ache. SSRIs have the potential to reason an obtained hemostatic defect related to their capacity to inhibit platelet characteristics. Especially, SSRIs inhibit the serotonin transporter on platelets, causing a lower in intra platelet serotonin and diminished remarks activation at some point of dense granule secretion, leading to intracranial hemorrhage (ICH). [2]

SSRI use may additionally affect ICH results. In ischemic stroke, pre-stroke SSRI use has been related to elevated 30-day mortality and decrease prices of discharge to home, but these findings have now not been reproduced. Current clinical trials located inconsistent efficacy of fluoxetine initiation after

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ischemic stroke for lengthy-time period motor healing. but, little data exist to guide SSRI use in ICH. [3]

This work aims to determine the safety of utilization of Selective Serotonin Reuptake Inhibitors (SSRI), regarding the incidence of intracranial hemorrhage.

Literature Review

Our review came following the (PRISMA) statement guidelines. [4]

Study eligibility

The included studies should be in English, a journal published article, and a human study describing intra-cranial hemorrhage patients. The excluded studies were non-English or animal studies.

Study identification

Basic searching was done over the PubMed, Cochrane library, and Google scholar using the following keywords: Intracranial Hemorrhage, Selective Serotonin Reuptake Inhibitors.

Data extraction and synthesis

RCTs, clinical trials, and comparative studies, which studied the outcome of the SSRI users group versus the Non-SSRI users' group of patients, will be reviewed. Outcome measures included the incidence of intracranial hemorrhage as the main primary outcome.

Study selection

We found 211 records, 106 excluded because of the title; 105 articles are searched for eligibility by full-text review; 56 articles cannot be accessed; 23 studies were reviews and case reports; 7 were not describing functional outcome; the desired drug not used in 12 studies leaving 7 studies that met all inclusion criteria.

Statistical analysis

Pooled odds ratios (OR), Proportions (%), with 95% confidence intervals (CI) assessed, using a statistical package (MedCalc, Belgium). The meta-analysis process was established via I^2-statistics (either the fixed-effects model or the random-effects model), according to the Q test for heterogeneity.

Results

The included studies were published between 2002 and 2020. Regarding the type of included studies, 7 studies (out of 8 studies) were case-control studies, while 1 study was a cohort study [Table 1]. [3,5-10]

Regarding patients' characteristics, the total number of patients in all the included studies was 153323 patients, with 19010 patients in the SSRI users group, and 134313 patients in the Non-SSRI users' group, with an average age of (66.8) years [Table 1].

A meta-analysis study was done on 7 studies that described and compared the 2 different groups of patients; with an overall number of patients (N=153323) [Table 2]. [3,5-10]

Each outcome was measured by:

Odds Ratio (OR)

- For the incidence of intracranial hemorrhage.

Concerning the primary outcome measure, we found 7 studies reported the incidence of intracranial hemorrhage. I^2 (inconsistency) was 93.5%, Q test for heterogeneity ($p<0.001$), so random-effects model was carried out; with overall OR= 1.4 (95% CI=1.027 to 1.912) [Figure 1].

Table 1: Patients and study characteristics.

N	Author	Type of study	Number of patients			Age (average years)
			Total	SSRI users group	Non-SSRI users group	
1	Bak et al. [5]	Case-control	44765	2915	41850	66.8
2	Kharofa et al. [6]	Case-control	2441	229	2212	--
3	Huhtakangas et al. [7]	Case-control	676	38	638	66
4	Renoux et al. [8]	Case-control	92738	14929	77809	66.6
5	Scheitz et al. [9]	Case-control	6242	266	5976	70.1
6	Kubiszewski et al. [10]	Cohort	1279	281	998	71.3
7	Liu et al. [3]	Case-control	5182	352	4830	60.5

#Studies arranged via publication year.

Table 2: Summary of outcome measures in all studies.

N	Author	Primary outcome Intracranial hemorrhage	
		SSRI users group	Non-SSRI users group
1	Bak et al. [5]	515	4250
2	Kharofa et al. [6]	71	845
3	Huhtakangas et al. [7]	7	51
4	Renoux et al. [8]	588	2448
5	Scheitz et al. [9]	13	253
6	Kubiszewski et al. [10]	36	40
7	Liu et al. [3]	146	2141

Using the fixed-effects model, the meta-analysis process revealed a significant increase in the incidence of intracranial hemorrhage in the SSRI users group compared to the Non-SSRI users' group (p=0.033) [Figure 2].

Discussion

This work aims to determine the safety of utilization of Selective Serotonin Reuptake Inhibitors (SSRI), regarding the incidence of intracranial hemorrhage.

The included studies were published between 2002 and 2020. Regarding the type of included studies, 7 studies (out of 8 studies) were case-control studies, while 1 study was a cohort study.

Regarding patients' characteristics, the total number of patients in all the included studies was 153323 patients, with 19010 patients in the SSRI users group, and 134313 patients in the Non-SSRI users' group, with an average age of (66.8) years.

A meta-analysis study was done on 7 studies that described and compared the 2 different groups of patients; with an overall number of patients (N=153323)

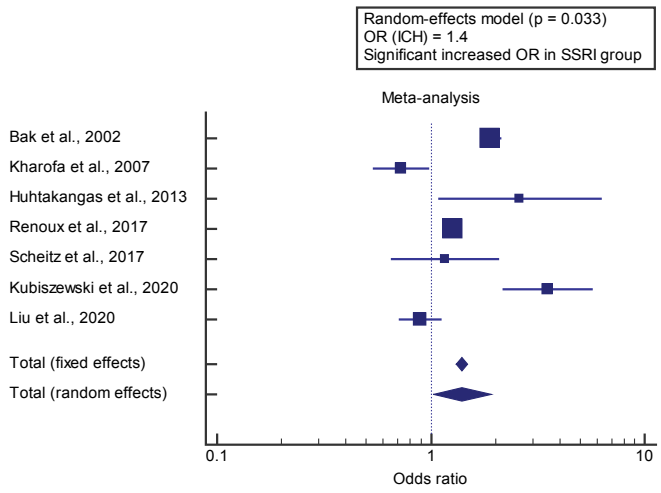

Figure 1: Forest plot (Intra-cranial hemorrhage).

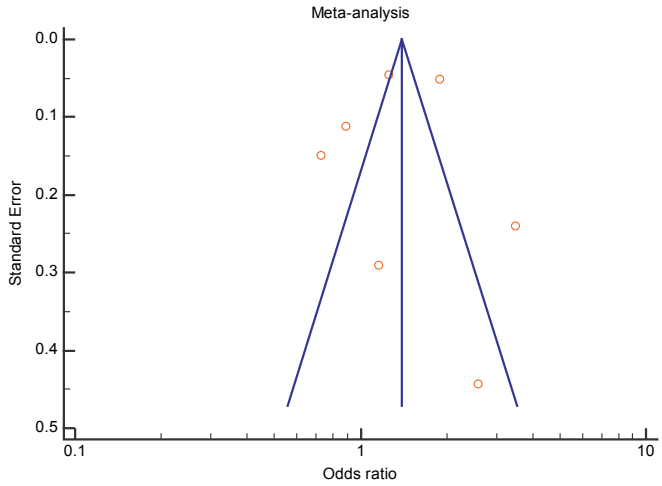

Figure 2: Funnel plot (Intra-cranial hemorrhage – A significant publication bias).

Concerning the primary outcome measure, we found 7 studies reported the incidence of intracranial hemorrhage. Using the fixed-effects model, the meta-analysis process revealed a significant increase in the incidence of intracranial hemorrhage in the SSRI users group compared to the Non-SSRI users' group (p=0.033), which came in agreement with Chollet et al., [11] Hackam & Mrkobrada, [12] Qureshi et al., [13] Teoh et al., [14] Izak & Bussel, [15] Catangui, [16] Kubiszewski et al., [10] Liu et al. [3] and Tully et al. [17]

Chollet et al. reported that, as serotonin is involved in platelet aggregation, a possible increased risk of bleeding complications, including intracerebral bleeding, probably as a result of inhibition of platelet aggregation. [11]

Qureshi et al. reported that Intracranial hemorrhage was related to SSRI exposure in bot unadjusted (RR 1.48) and changed analyses (RR 1.51). Intracerebral hemorrhage became additionally related to SSRI exposure in each unadjusted (RR 1.68) and adjusted (RR 1.42) analysis. In a subset of 5 research (three of intracranial hemorrhage and 1 each reporting hemorrhagic stroke and intracerebral hemorrhage), SSRI publicity in combination with oral anticoagulants was related to an accelerated hazard of bleeding in comparison with oral anticoagulants alone (RR 1.56). [12]

Hackam & Mrkobrada reported that, of their affected person with reversible cerebral vasoconstriction syndrome (RCVS) syndrome, providing with thunderclap-like headache, there is a possibility to be quite simply confused with a migraine. Initiating treatment with selective serotonin reuptake inhibitors (SSRIs) and triptans can similarly worsen the situation. consequently, it's far vital to understand the nature and form of headache and correlate the medical findings with imaging studies. [13]

Teoh et al. reported that there's growing literature that associates serotonergic antidepressants with an improved hazard of bleeding. SSRIs have been related to oral adverse results relating to bleeding, consisting of prolonged bleeding time, petechiae, ecchymosis, bruising and gingival bleeding. The proposed mechanism by which this happens is via the inhibition of serotonin reuptake into platelets. Serotonin, in conjunction with other factors along with ADP and prothrombin, potentiates platelet aggregation. [14]

Izak & Bussel reported that the list of medications interfering with platelet function includes beta-lactam antibiotics, nitrates, beta-blockers, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and others, most of them only *in vitro*, having unclear clinical significance, that increase intracranial hemorrhage. [15]

Catangui reported that Selective serotonin reuptake inhibitors or serotonin-specific reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) increased the risk of bleeding. [16]

Kubiszewski et al. reported that the mean age of study contributors was 71.3 years, with 602 girls (47%); of the 1279 participants, 1049 had been White, 89 had been Black, 77

were Hispanic, and 64 have been of other race/ethnicity. SSRI exposure became related to each ICH recurrence (RR, 1.31) and resolution of publish-ICH depression (RR, 1.53). amongst those individuals at high threat for recurrent ICH, SSRIs have been related to further elevation in threat for ICH recurrence (RR, 1.79) in comparison with all different survivors of ICH (RR, 1.20; P<0.01 for a contrast of effect sizes). The association of SSRI with reduced depressive signs and symptoms did not differ between excessive the ones at excessive threat for recurrent ICH and all other ICH survivors. [10]

Liu et al. reported that the cohort consisted of 2287 ICH cases and 2895 controls. Pre-ICH SSRI use became now not related to ICH danger (OR, 0.824) nor potentiation of ICH danger with anticoagulant or antiplatelet use. New publish-ICH SSRI use changed into related to unfavorable modified Rankin Scale score at 3 months after ICH (OR, 1.67 P<0.01) in multivariable analyses. Extra propensity rating evaluation indicated a comparable trend but did not reach statistical significance (P>005). [3]

Tully et al. reported that the study suggested that antidepressant use for<6 months increased stroke risk, while spontaneous intracranial hemorrhage is a risk among SSRI users particularly in the first 30 days of use and when used concomitantly with oral anticoagulants. [17]

Conclusion

To conclude, SSRIs exposure after ICH is associated with both improvement in depressive symptoms and increased risk of recurrent hemorrhagic stroke. Clinical history, neuroimaging data, and genetic biomarkers may help to identify survivors of ICH more likely to safely tolerate SSRI use.

Competing Interests

The authors declare that they have no competing interests. All the listed authors contributed significantly to the conception and design of study, acquisition, analysis, and interpretation of data and drafting of the manuscript, to justify authorship.

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