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Research Article

Selective serotonin reuptake inhibitors and the risk of bleeding

Padma L[1], Ranjani Ramanujam[1,*], Rohini S. Thimmaiah[2]

[1]Department of Pharmacology, Dr. B. R. Ambedkar Medical College, Bangalore-560045, India, [2]Department of Psychiatry, Dr. B. R. Ambedkar Medical College, Bangalore-560045, India

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***Correspondence to:**
Dr. Ranjani Ramanujam,
Email: ranjani.mohan@gmail.com

ABSTRACT

Background: Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed agents for various conditions in general psychiatry. There is a strong consensus that blockade of serotonin reuptake affects primary hemostasis, namely platelet activity, thus resulting in a bleeding tendency. Considering that SSRIs are commonly prescribed, this study was conducted to assess if they were associated with an increased risk of bleeding.
Methods: This was a prospective, open-label study of 30 patients attending the Psychiatry out-patient department, Dr. B. R. Ambedkar Medical College, Bangalore who satisfied DSM-IV criteria for a primary diagnosis of depression, treated with SSRIs. Bleeding time, clotting time, prothrombin time, partial thromboplastin time and platelet count were assessed at baseline and at the end of 6 weeks of treatment or occurrence of bleeding symptom.
Results: The patients aged between 18-55 years of whom 21 were females, were treated with an SSRI (fluoxetine 12, escitalopram 12 and sertraline 6 patients). Six patients had overt symptoms of bleeding (upper gastrointestinal bleeding (hematemesis) 4; epistaxis 2 and petechiae 2) of whom one patient gave a history of both hematemesis and petechiae and another of hematemesis and epistaxis. The average day after treatment beginning, on which patients reported with bleeding was 30.33 (26-40 days). There was a significant increase in the bleeding time (p=0.028) and clotting time (p=0.042), implying derangement in platelet aggregation. There was no significant change in the other parameters.
Conclusion: Treatment with SSRIs increases the risk of bleeding. However, large, randomized controlled trials are required to re-affirm these findings.

Keywords: SSRIs, Bleeding time, Clotting time

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are one of the most widely prescribed classes of drugs in psychiatry,[1] used in the management of varied psychiatric disorders including depression, obsessive-compulsive disorder, generalized anxiety disorder, panic disorder, post-traumatic stress disorder and premenstrual dysphoric disorder.[2]

Owing to the fact that they are extensively used, their impact of relatively infrequent yet serious side-effects is of potential clinical importance. One such side-effect is an increased bleeding tendency.[1]

Andrade et al.[3] describe several mechanisms that might be responsible for bleeding with the use of SSRIs: (i) inhibition of serotonin uptake into platelets: serotonin reuptake inhibitors inhibit serotonin transporter (SERT), as a result of which they prevent the reuptake of serotonin presynaptically and also from blood into platelets. The platelets do not synthesise serotonin, but release the serotonin which has been taken up from the blood, in response to vascular injury, which triggers vasoconstriction and platelet aggregation. When the SERT is inhibited, the platelets have inadequate stores of serotonin, because of which there is a resultant increase in risk of bleeding; (ii) increase in gastric acid secretion: SSRIs directly increase the gastric acid secretion, which has an ulcerogenic effect, and resultant GI bleeding; (iii) other mechanisms: certain SSRIs (fluoxetine, paroxetine and fluvoxamine) are potential inhibitors of cytochrome P450, because of which there is a reduced metabolism and therefore, increased plasma levels of drugs like NSAIDs, antiplatelet drugs and other drugs metabolized

by these enzymes, if concomitantly administered. This results in increased risk of bleeding.

There have been several contradicting reports on the association of SSRI use and bleeding. Therefore, we undertook the current study to assess if patients on SSRIs were at an increased risk of bleeding.

METHODS

The current study was a prospective, open-label study conducted between September 1, 2011 and February 29, 2012 in Dr. B. R. Ambedkar Medical College and Hospital, Bangalore. Patients ≥18 year attending the Psychiatry out-patient department who satisfied DSM-IV-TR criteria for a primary diagnosis of depression, treated with SSRIs were included in the trial. Exclusion criteria included patients with any bleeding disorders, on concomitant medications like NSAIDs, antiplatelet and anticoagulant therapy and with any comorbid illnesses. Pregnant and lactating women were also excluded from the study. Informed consent was taken from all patients and ethical clearance was obtained from the Institutional Ethics Committee.

The parameters assessed were bleeding time, clotting time, prothrombin time, activated partial thromboplastin time and platelet count. The assessments were done at baseline and at the end of 6 weeks of treatment or occurrence of bleeding symptom.

Statistical significance calculated using Wilcoxon signed-rank test. Statistical analysis was done using SPSS software Ver. 16.

RESULTS

A total of 30 patients were included in the study, of whom 21 were females. The average age was 33.3 years (Range: 18-55 years). The details of the SSRI prescribed are shown in Figure 1.

There were 8 events related to overt bleeding in a total of 6 patients. Upper gastrointestinal bleeding presenting as hematemesis was the most common event, present in four patients. There were two events each of epistaxis and petechial hemorrhages on the legs. One patient had concomitant epistaxis and another had petechiae along with upper GI bleeding.

All the symptoms were mild. Patients presenting with hematemesis and epistaxis had reported after the first episode itself. The average day of reporting of bleeding symptom was the 30th day (Range: 26-40 days).

With respect to the laboratory parameters assessed, there was a significant increase in bleeding time and clotting time in patients with bleeding event (Table 1). There was no significant change in the other parameters assessed like prothrombin time, activated partial thromboplastin time and platelet count in the symptomatic group.

Additionally, there was no significant change in all parameters in the remainder of patients who completed the trial for 6 weeks.

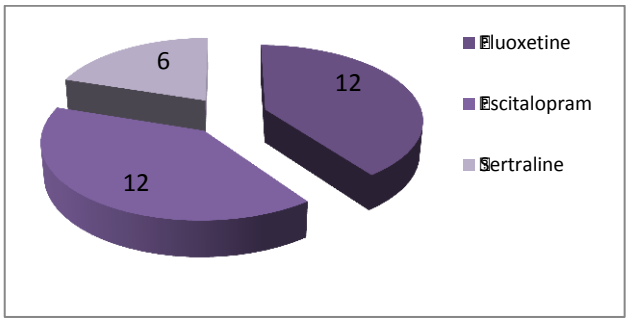

Figure 1: Specific SSRI prescribed.

Table 1: Bleeding and clotting times in patients with bleeding event.

Parameter	Baseline	At presentation with bleeding symptom	*p* value
Bleeding time (seconds)	181.66 (160-200)	381.66 (310-450)	0.028*
Clotting time (seconds)	395 (280-690)	653.33 (560-750)	0.042*
* $p<0.05$ considered statistically significant			

In patients who reported with a bleeding event, the drug was discontinued immediately. Patients with hematemesis were prescribed a proton pump inhibitor. They were started on alternate non-SSRI antidepressants (e.g., mirtazapine, venlafaxine), and followed up at least for the rest of the study period, during which there was no recurrence of symptoms.

DISCUSSION

In our study, SSRIs caused a significant increase in bleeding tendency, as assessed by an increase in the bleeding and clotting time. Upper GI bleeding presenting as hematemesis was the commonest bleeding manifestation observed with an incidence of 13.3% (n=4), followed by epistaxis and petechiae on the lower limbs (6.7%, n=2 each). There was a significant increase in the bleeding (p=0.028) and clotting times (p=0.042) in these patients compared to those who did not have a bleeding event.

However, there has been contradicting evidence on the association of abnormal bleeding with SSRI use. The overall risk appears to be small, yet significant.[3] Upper GI

bleeding is the most commonly reported bleeding abnormality reported with the use of SSRIs. In a study by de Abajo et al.,[4] the incidence of upper GI bleed was 1 per 8000 SSRI prescriptions. This was a large population based case-control study conducted in the UK, where there was a 15-fold increase in risk of gastrointestinal bleeding. Dalton et al.[5] demonstrated an increased risk of bleeding was seen in 3.1 patients per 1000 SSRI treatment years. However, in a more recent case-control study by Carvajal et al., there was no significant increase in risk in upper GI bleeding with SSRIs.[6]

Another important factor is the effect of concomitant drugs use on bleeding. When NSAIDs and SSRIs are given together, they seem to increase the risk of bleeding.[4,5,7,8] When used along with antiplatelet drugs like aspirin and clopidogrel, there have been mixed results, some showing an increased risk of bleeding,[4,5,7,9,10] while other not.[8,11]

Additional use of proton pump inhibitors has shown to reduce the risk of bleeding with SSRIs.[8,12]

However, there is a paucity of data on the association of SSRI intake and the risk of other types of abnormal bleeding. Additionally, research is required to determine if SSRIs are protective in patients with ischemic heart disease or ischemic stroke, and also if they increase bleeding in patients with a higher risk of hemorrhagic stroke.

The limitations of our study were that it was an open-label, single arm study with no control or comparator, the sample size was small and the duration of follow-up was short.

According to our study, SSRIs are associated with an increased risk of bleeding, and this needs to be studied in a large population, since SSRIs are very frequently prescribed in psychiatric practice.

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