

Selective serotonin reuptake inhibitor use and intraoperative bleeding in urologic surgery

Abstract

Background: Selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed. The prescribing information for SSRIs acknowledges these medications may increase the risk of bleeding. However, few studies on SSRI use and intra operative bleeding have been conducted. The goal of this study is to determine if bleeding is increased in urologic surgical patients on SSRIs and if those patients have an increased need for blood transfusions.

Methods: A retrospective chart review was performed to collect age, preoperative hemoglobin, whether they were prescribed a SSRI (fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, or escitalopram) or aspirin (ASA) at the time of surgery, if intra operative colloids were used, their estimated blood loss, and the amount of blood transfused (if applicable).

Results: The study included 181 patients, of which 20 were SSRI users. The average age was 62 years old, mean preoperative hemoglobin was 13.6g/dL, and 25% were ASA users. There was no significant difference in mean blood loss (877.5mL SSRIs; 873.6mL non-SSRIs; $p=0.9814$) or blood transfusions between groups ($p=0.6130$). ASA or intra operative colloid use significantly affected the amount of blood loss ($p<0.0001$). There was a significantly lower preoperative hemoglobin in patients requiring transfusions ($p=0.0021$) and a significantly higher percentage of transfusions required in ASA users ($p=0.0024$).

Conclusion: No association was found between the use of SSRIs and perioperative blood loss or blood transfusions. However, ASA or intra operative colloid use could increase the amount of blood loss, and lower preoperative hemoglobin levels or ASA use may increase patients' need for blood transfusion.

Keywords: selective serotonin reuptake inhibitors, intraoperative, bleeding

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Abbreviations: ANOVA, analysis of variance; ASA, aspirin; CPT, current procedural terminology; GI, gastro intestinal; IRB, information security officer; IRB, institutional review board; R&D, research & development; SSRIs, selective serotonin reuptake inhibitors (SSRIs); 5-HT_{2A}, serotonin receptors; SERT, serotonin transporters; SPSS, statistical package for the social sciences; VISTA, veterans health information systems and technology architecture

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed to treat psychiatric diseases such as depression, post-traumatic stress disorder, anxiety, obsessive-compulsive disorder, and panic disorder. Research has found that platelets contain serotonin receptors (5-HT_{2A}) and serotonin transporters (SERT) which prime platelet activation and pro-coagulant responses. More specifically, when platelets are activated, calcium is released within the platelet causing degranulation of serotonin from δ -granules.^{1,2} This circulating serotonin is then either taken back up into the platelet via SERT or it can bind to 5-HT_{2A} receptors. When serotonin binds to 5-HT_{2A} receptors it causes additional calcium release, further activating platelets to cause thrombin generation and clot formation. It is established that SSRIs, which decrease serotonin uptake into the central nervous system, can also decrease serotonin uptake into platelets, reducing rates of platelet aggregation and thrombus formation. Furthermore, the prescribing

information for SSRIs state that bleeding events related to SSRIs have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.³

Bleeding due to SSRIs has been discussed in multiple case reports and clinical trials leading to the conclusion that SSRIs increase the risk of upper gastrointestinal (GI) bleeds.⁴ Conceptually, the same SSRI process that causes an increased risk of upper GI bleeding should cause an increased risk of intra operative bleeding. However, minimal studies on SSRI use and bleeding have been conducted in surgery, and the studies published are inconsistent. These few studies focused on orthopedic surgery, post-coronary artery bypass graft, and post-surgical breast cancer removal.⁵⁻⁸ The risk of intra operative bleeding due to SSRIs has not been evaluated extensively in surgeries, and to our knowledge, there are no studies looking at this danger in urologic surgery. The objective of this study was to determine the association between use of SSRIs and perioperative blood loss in urologic surgical patients.

Materials and methods

This retrospective study was conducted at James A. Haley Veterans' Hospital, a large teaching hospital in Tampa, FL. The Research & Development (R&D), Institutional Review Board (IRB), and Information Security Officer (ISO) approved the study protocol. The study population consisted of all patients who underwent a

cystoprostatectomy, simple prostatectomy, or a radical prostatectomy during the period of January 1, 2005 to December 31, 2011. Patients were identified by means of a computerized report generated from the Veterans Health Information Systems and Technology Architecture (VistA) program that selected patients based on a database search using current procedural terminology (CPT) codes standardized by the American Medical Association. The CPT codes used to identify the aforementioned medical records include 55840, 55842, 55845, 55866, 55831, 51590, 51595, and 51596.

The patients identified through the CPT code search were reviewed for inclusion/exclusion criteria. The first 200 patients identified who met both criteria were included in this research. Patients were included if they underwent either a cystoprostatectomy, simple prostatectomy, or a radical prostatectomy during January 1, 2005 to December 31, 2011 and were either prescribed an SSRI or no antidepressant. Patients were excluded from the study if

- a. They were prescribed an antidepressant other than an SSRI (fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, or escitalopram)
- b. Had a preexisting bleeding disorder
- c. Did not hold clopidogrel for at least 5days prior to surgery
- d. Received warfarin prior to surgery and INR was greater than 1.2 on the day of surgery
- e. Did not hold fondaparinux for at least 36hours prior to surgery
- f. Did not hold enoxaparin for at least 24hours prior to surgery
- g. Did not hold heparin 3hours prior to surgery.⁹⁻¹¹

The primary objective was to determine the relationship between SSRI use and estimated intra operative blood loss during urologic surgery. The secondary objective was to establish whether patients on SSRIs have an increased need for blood transfused.

Data collected during chart review consisted of the patients' age, pre-operative hemoglobin level, whether they were prescribed an SSRI at the time of surgery, if they were actively taking aspirin (ASA) at the time of surgery, whether they received intra operative colloid, their estimated blood loss, and the amount of blood transfused (if applicable). Estimated blood loss was calculated by the anesthesia team: the amount of blood vacuumed into a container plus the number of surgical lap sponges [times 80ml] plus the number of Ray-Tec sponges [times 15ml] minus the amount of irrigation used. Although the amount of blood loss is an estimate, it is standard practice and the only way the facility measures this parameter.

The sample size was determined from the estimated number of cystoprostatectomy, simple prostatectomy, and radical prostatectomy procedures performed within the previous sevenyears. Baseline characteristics of all patients were described as proportions or means±standard deviation as appropriate. Two sample t' test was performed to determine the significance of differences in the means of estimated blood loss between SSRI users and nonusers. Multivariate linear regression model was used to control for multiple covariates (ex. age, hemoglobin level, surgery type, etc.) when looking at the association between the use of SSRIs or nonusers and intra operative blood loss. Analysis of variance (ANOVA) was used to determine if there was a difference in blood loss between surgery types. The association between SSRI use and the need for blood transfusion

was evaluated by means of a chi-square test and a univariate logistic regression model. Lastly, the relationship between preoperative hemoglobin level and the need of blood transfusion was assessed using the two sample t-test and the correlation between ASA use and the need of blood transfusion was reviewed with a chi-square test. SPSS (Statistical Package for the Social Sciences) was used to run these statistics.

Results and discussion

A total of 181 patients were included in the study. Amongst the first 200 patients identified according to protocol, few were excluded due to concomitant use of either trazodone (n=9), bupropion (n=5), amitriptyline (n=3), or venlafaxine (n=2). The average age of the population was sixty-two years (min=42, max=92) with a mean preoperative hemoglobin level of 13.6g/dL. At the time of surgery, twenty patients were prescribed an SSRI: citalopram (n=9), fluoxetine (n=2), fluvoxamine (n=1), paroxetine (n=4), and sertraline (n=4). It should be noted that 25% (n=46) of the total population were actively taking ASA at the time of surgery. A majority of the patients included in the study underwent a radical prostatectomy (66.85%), whereas the rest underwent either a cystoprostatectomy or simple prostatectomy (27.62% or 5.52%, respectively) (Table 1).

Table 1 Baseline characteristics (N=181)

Age	
Mean (SD)	61.5±8.4
Min	42
Max	92
Surgery type	
Cystoprostatectomy	50 (27.62)
Radical Prostatectomy	121 (66.85)
Simple Prostatectomy	10 (5.52)
Pre-Op Hemoglobin Level	
Mean (SD)	13.6 (1.6)
SSRI	
Yes	20 (11.05)
Citalopram	9
Fluoxetine	2
Fluvoxamine	1
Paroxetine	4
Sertraline	4
No	161 (88.95)
ASA	
Yes	46 (25.41)
No	135 (74.59)

Data is expressed as means±SD or n (%).

When comparing SSRI users to non-SSRI users, there was no significant difference in the amount of blood lost (877.5mL for users and 873.6mL for non-users; $p=0.9814$) and no significant difference in the need of blood transfusion ($p=0.6130$). When controlling for confounding variables (e.g. age, pre-op hemoglobin, ASA use, surgery type, and intra operative colloid use), only ASA use and intra operative colloid use significantly affected the amount of blood loss within the total population (<0.0001). Although not statistically significant, patients who underwent a radical prostatectomy had a greater chance of having a larger amount of blood loss ($p=0.1198$) compared to both simple prostatectomy and cystoprostatectomy (Figure 1). When looking further into the need of blood transfusions, an average of two units (range 1-6) of packed red blood cells was administered to patients who required a transfusion. Some observational results found were that the average preoperative hemoglobin level was significantly lower in patients requiring blood transfusions ($p=0.0021$) (Figure 2) and the percentage of patient's requiring transfusions was significantly higher in ASA users compared to ASA non-users (58.7% vs. 33.3%; $p=0.0024$) (Figure 3).

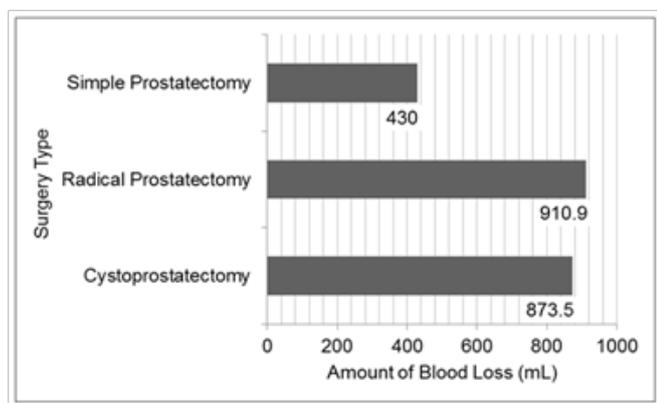


Figure 1 Blood Loss per Surgery

*No significant difference ($p=0.1198$)

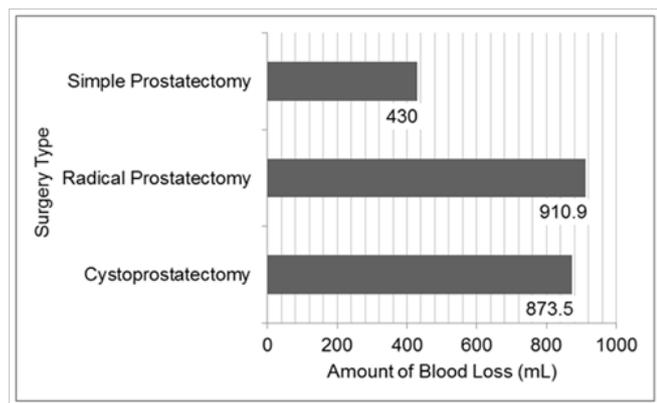


Figure 2 Hemoglobin Level vs. Blood Transfusion Requirements.

*Significant Difference ($p=0.0021$)

Urologic surgical procedures were chosen because they have never been studied in reference to SSRI bleeding. Furthermore, the three specific urological procedures were chosen due to their high bleeding potential, procedure frequency, and to minimize differences in surgical techniques. Another reason for choosing urologic

surgical procedures was their independence from cell saver devices, tourniquets, perfusion machines, or intra operative anticoagulation. The present study did not find an association between the use of SSRIs and perioperative blood loss or transfusion in urologic surgical patients. Although this study did not reveal any difference, there are several articles indicating that SSRIs may increase perioperative blood loss. One study concluded SSRIs increase blood loss and the need for blood transfusions amongst orthopedic patients.⁸ However, another orthopedic study demonstrated a statistically significant increase in blood loss with SSRI users that were not clinically significant and there was no increase in the need for blood transfusions.⁵ The results of the aforementioned trials demonstrate the clinical significance of the hypothesis may be minimal and more studies resemble the results of the current study. No significant increase in blood loss was found in a study comparing SSRI users to non-SSRI users undergoing coronary artery bypass grafting surgery.⁷ However, this study allowed for concurrent use of other anti-platelets and anticoagulants which could explain the insignificance in their study due the minimal anti-platelets effects of SSRIs compared to these other agents. Evaluating the effect SSRIs have on blood loss and the need for transfusions based on the whole body of literature, including this study, leads to inconclusive results. There are a few limitations with the current protocol. The proportion of SSRI users amongst the entire population was smaller than anticipated. Laparoscopic prostatectomies were included within the radical prostatectomy group, and laparoscopic surgical procedures are intended to have less blood loss than open procedures. Although the veterans' hospital utilizes an electronic medical record that includes the complete medication list and refill history, patients have the ability to obtain medications from outside sources, and the hospital relies on the patients to inform them of such medications. Surgical technique amongst various surgeons can affect blood loss, which was not accounted for. Newer guidelines established in 2007 recommend ASA are continued throughout non-cardiac surgery in patients with heart stents. Therefore, surgeries prior to 2007 may have less bleeding since clinical practice supported stopping ASA prior to surgery.¹² There are confounding variables throughout surgery, besides those included in the analysis that cannot be accounted for as they vary by patient. Particularly, perioperative patient stress and depression have been found to possibly increase the risk of bleeding.¹³

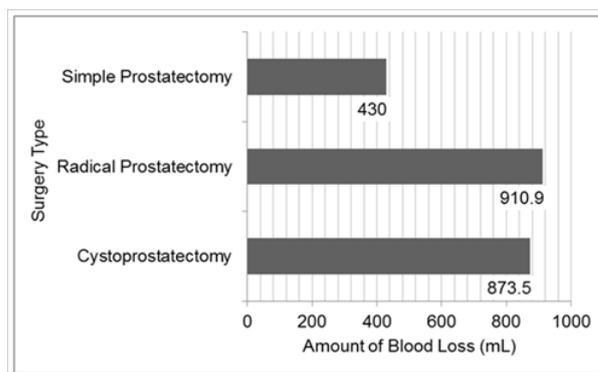


Figure 3 ASA Use vs. Blood Transfusion.

*Significant Difference ($p=0.0024$)

Conclusion

No association was found between the use of SSRIs and perioperative blood loss or blood transfusions in urologic surgery.

It was observed that ASA use or intra operative colloid use could increase the amount of blood loss. It was also observed that lower preoperative hemoglobin levels or ASA use may increase the need for blood transfusion. Further studies, preferably prospective trials, are required to accurately determine whether SSRIs increase the risk of intra operative blood loss and the need for blood transfusions.

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Conflict of interest

The author declares no conflict of interest.

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