Clinical Investigations

Safety of Selective Serotonin Reuptake Inhibitor Use Prior to Coronary Artery Bypass Grafting

Address for correspondence:
Glen L. Xiong, MD
University of California,
Davis School of Medicine
Department of Psychiatry and
Behavioral Sciences
Department of Internal Medicine
2230 Stockton Blvd.
Sacramento, CA 95817-1419
gxiong@ucdavis.edu

Glen L. Xiong, MD; Wei Jiang, MD; Robert M. Clare, MS; Linda K. Shaw, MS; Peter K. Smith, MD; Christopher M. O'Connor MD; K. Ranga R. Krishnan, MD; L. Kristin Newby, MD, MHS
Department of Internal Medicine (Ziong, Jiang, O'Connor, Newby) University of California, Davis, California; Department of Psychiatry (Xiong, Jiang, Krishnan), Duke University Medical Center, Durham, North Carolina; Duke Clinical Research Institute (Clare, Shaw, Smith, O'Connor, Newby), Duke University Medical Center, Durham, North Carolina; Department of Surgery, Division of Cardiothoracic Surgery (Smith), Duke University Medical Center, Durham, North Carolina; Division of Cardiology (O'Connor, Newby), Duke University Medical Center, Durham, North Carolina.

ABSTRACT

Background: Selective serotonin reuptake inhibitors (SSRIs) have been shown to increase bleeding risks. This study examined the association of perioperative coronary artery bypass grafting (CABG) bleeding risks and SSRI use prior to CABG.

Hypothesis: SSRI may be associated with increased bleeding risks after CABG resulting in elevated reoperation rates due to bleeding complications.

Methods: Patients who underwent CABG between 1999 and 2003 (n = 4794) were identified in a tertiary medical center. SSRI use (n = 246) was determined using inpatient pharmacy records. Outcomes included primary end point of reoperation due to bleeding complications and other secondary measures. Multivariate regression models were constructed to adjust for baseline differences between SSRI and control groups.

Results: Reoperation due to bleeding complications among SSRI users was not significantly different (odds ratio [OR]: 1.14 (0.52–2.47); $P = 0.75$) compared to the control group. Other secondary outcomes and 30-day mortality (2.0% in SSRI vs 2.1% in control group; $P = 0.92$) between the 2 groups were similar. However, the adjusted total volume of postoperative red blood cell (RBC) units transfused was higher in the SSRI group.

Conclusion: We conclude that there is no compelling evidence to limit the use of SSRIs among patients with coronary artery disease who undergo CABG given the current evidence. Further research may be needed on individual SSRI medications.

Introduction

Given the high comorbidity of depression and coronary artery disease (CAD), selective serotonin reuptake inhibitors (SSRIs) are used for the treatment of depression in the patient with CAD and prior to coronary artery bypass grafting (CABG).[1–3] We previously reported that SSRI use before CABG was associated with a higher long-term risk of rehospitalization and death.[4] Although the explanation for these findings is unclear, whether SSRI use may result in bleeding complications immediately after CABG is a concern. SSRIs have antiplatelet activity and reduces the release of platelet factor 4, β-thromboglobulin, and P-selectin.[5–7] Clinically, SSRIs have been linked to increased upper gastrointestinal bleeding in several population-based retrospective studies.[8–11] In these studies, the risks appeared to be higher among patients taking other antiplatelet medications.[12–14] In a small study of patients undergoing orthopedic surgery, the odds for red blood cell (RBC) transfusion were almost 4 times higher among SSRI-treated patients compared with the control group.[15] However, this association was not observed in a Danish study of SSRI use among CABG patients.[16] This particular study has not been replicated. Therefore, clinical concerns persist especially in light of the new guidelines from the American Heart Association to improve depression screening and treatment in patients with coronary artery disease, many of whom may require CABG.[17,18]

This study examined patients who underwent CABG for the association of preoperative SSRI administration with the need for reoperation due to bleeding complications,

This study was supported in part by an unrestricted research grant from Bristol-Myers Squibb-Sanofi Pharmaceuticals to LKN.

Clin. Cardiol. 33, 6, E94–E98 (2010)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20621

Received: March 17, 2009
Accepted with revision: April 9, 2009

use of postoperative RBC transfusion, and a composite end point (reoperation for bleeding complications, postoperative hematocrit drop of $> 15\%$, or postoperative RBC transfusion).

Methods

Patient Population and Data Collection

Patients who underwent CABG-only procedures between January 1, 1999 and December 31, 2003 ($n = 4794$) were identified from the Duke Databank for Cardiovascular Disease, an ongoing registry of patients who have undergone a cardiac procedure at Duke University Medical Center since 1969.[19] Exposure to SSRI antidepressants prior to CABG was determined from inpatient pharmacy records during index hospitalization. SSRIs included fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram, venlafaxine, and clomipramine due to their potent serotonergic activity.[20] Further details about this patient population, selection criteria, and patient outcomes were previously published.[2] The institutional review board at Duke University Medical Center approved the study protocol.

Clinical Outcomes

The bleeding end points for this study were selected a priori after discussion among the study investigators and based on review of the literature.[21] The primary end point was the need for reoperation due to any bleeding complications. Because numerous CABG-related bleeding end points are reported in the literature, relationships with several other key secondary bleeding end points were also explored, including any need for postoperative RBC transfusion and a composite end point that captured reoperation for bleeding complications, postoperative hematocrit drop of $\geq 15\%$, or any postoperative RBC transfusion. We also examined the relationship of SSRI use with individual end points of hematocrit drops $\geq 15\%$ or $\geq 30\%$, percentage change of hematocrit from baseline, need for transfusion of other individual blood products, and total units of RBC transfused, and 30-day mortality.

Statistical Analysis

Baseline characteristics are described using medians with 25th and 75th percentiles for continuous variables and proportions for categorical variables. Unadjusted rates of the various bleeding end points by SSRI use are presented. Unadjusted comparisons were made using the χ^2 test for proportions and Wilcoxon rank sum test for continuous variables. Adjusted associations of SSRI use with bleeding outcomes are presented as odds ratios (OR) with 95% confidence intervals (CI). Strength of association was estimated using the magnitude of the Wald χ^2 test. A P value of < 0.05 was considered statistically significant. To account for nonrandom treatment assignment, a propensity score was constructed using logistic regression to estimate the probability of SSRI use as a function of baseline characteristics.[22] The propensity score models the "risk" of SSRI use prior to CABG. The propensity score is based on demographic variables (age, ethnicity, gender, smoking history, family history of CAD), medical disorders (diabetes, hypercholesterolemia, hypertension, chronic lung disease, New York Heart Association failure class, myocardial infarction, cardiogenic shock, etc.), and medication use (aspirin, β-blockers, angiotensin-converting enzyme inhibitors, etc.) that may have increased the odds of SSRI use.[4] The C-index (a measure of reliability for the propensity score) was 0.712.

Covariates for the baseline logistic regression models for primary and secondary bleeding end points were derived by stepwise selection, as detailed elsewhere.[19] The final model covariates for the outcomes included weight, prior myocardial infarction, heparin on day of surgery; for the RBC transfusion end point the model included clopidogrel use ≤ 5 days before surgery, age, sex, hypercholesterolemia, number of diseased vessels, baseline hematocrit >36, creatinine clearance, urgent procedure status, on-pump procedure, use of glycoprotein IIb/IIIa antagonists, and which surgeon performed the procedure. The covariates for the linear regression model for volume of RBC units transfused included clopidogrel ≤ 5 days before surgery, age, gender, smoker, hypercholesterolemia, peripheral vascular disease, congestive heart failure, angina, number of diseased vessels, procedure status urgent, cardiopulmonary bypass used, and surgeon.

Results

Of 4794 CABG patients included in our analysis, 246 (5.1%) were taking SSRIs prior to CABG. The baseline characteristics of the SSRI and control (no SSRI) groups are shown in Table 1. Compared with control patients, patients taking SSRIs were more frequently white and female, had more medical comorbidities, and had more urgent CABG procedures. Aspirin and anticoagulant use were more common and baseline hemoglobin and creatinine clearance were lower in the SSRI group.

Unadjusted comparisons of bleeding end points between SSRI and control groups are shown in Table 2. Rates of reoperation for bleeding were low in both groups and were not significantly different. Rates of RBC transfusion were high in both groups (70.7% and 68.2% in the SSRI and control groups, respectively), but were not significantly different ($P = 0.41$). However, among those receiving transfusions, the median volume of RBC units transfused was higher in the SSRI group (5.0 [3.0, 7.0] units) than the control group (4.0 [2.0, 6.0] units; $P < 0.001$). No significant difference was observed in the composite end point between groups. Further, 30-day mortality was low and did not differ between groups (2.0% in the SSRI group vs 2.1% in control; $P = 0.92$).

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20621

Table 1. Baseline Characteristics of SSRI vs Non-SSRI Groups Prior to CABG

	No SSRI (n = 4548)	SSRI (n = 246)
Age	64 (56–72)	63 (54–72)
White	3473 (76.36%)	211 (85.77%)
Female	1325 (29.13%)	108 (43.90%)
Smoker	2262 (49.74%)	119 (48.37%)
Diabetes	1553 (34.15%)	114 (46.34%)
Hypercholesterolemia	2549 (56.05%)	166 (67.48%)
Hypertension	3159 (69.46%)	198 (80.49%)
Cerebrovascular Disease	517 (11.37%)	46 (18.70%)
Preoperative Medications		
Aspirin	3474 (76.39%)	205 (83.33%)
Heparin	3542 (77.88%)	234 (95.12%)
Glycoprotine IIb/IIIa antagonist	728 (16.01%)	59 (23.98%)
Operative Parameters		
Number of Disease Vessels		
1	270 (5.94%)	20 (8.13%)
2	806 (17.72%)	50 (20.33%)
3	3472 (76.34%)	176 (71.54%)
Urgency of Procedure		
Elective	1780 (39.14%)	55 (22.36%)
Urgent	2560 (56.29%)	178 (72.36%)
Emergent	200 (4.40%)	13 (5.28%)
Laboratory Studies		
INR	1.10 (1.10, 1.30)	1.10 (1.00, 1.20)
PTT	31.30 (26.60, 45.10)	29.20 (25.50, 42.10)
Platelet	199 (163, 243))	210 (179, 257)
Hemoglobin	13.20 (11.60, 14.40)	12.50 (11.20, 14.00)
Hematocrit	40.00 (35.00, 43.00)	38.00 (34.00, 42.00)
Creatinine clearance	82.74 (61.11, 107.8)	79.89 (57.74, 106.1)

Abbreviations: CABG, coronary artery bypass graft; INR, international normalized ration; PTT, partial thromboplastin time; SSRI, selective serotonin reuptake inhibitor.

As shown in Table 3, after adjustment for baseline characteristics associated with the primary and secondary bleeding end points, the use of SSRIs prior to CABG was not significantly associated with increase odds of adverse events for reoperation for bleeding complications (OR: 1.14, 95% CI: 0.52–2.47); for any RBC transfusion (OR: 1.04, 95% CI: 0.75–1.44), and for the composite end point (OR: 1.21, 95% CI: 0.67–2.19). Despite adjusting for baseline factors, the previously noted difference in higher volume of RBC units transfused in the SSRI group (displayed in Table 2) persisted. The adjusted total units of postoperative RBC units transfused was 6.1 units in the SSRI group vs 5.2 units in the group that did not receive SSRI preoperatively ($P = 0.04$).

Discussion

Selective serotonin reuptake inhibitor use had been previously shown to be associated with upper gastrointestinal bleeding and increased odds of RBC transfusion in orthopedic surgery, but not in CABG. In a Danish study of 3454 patients who underwent CABG, of whom 3.5% (n = 124) were taking SSRIs before CABG, Andreasen et al found no evidence of increased bleeding risks in the SSRI group, including the end points of reoperation for bleeding, RBC transfusion, or mortality.[18] Our results are consistent with their findings and SSRIs do not appear to contribute to any adverse events after CABG.

In the Andreasen et al[16] study, the median volume of RBC transfused was lower among SSRI users than those not using SSRIs (3.0 vs 4.0 units, respectively; $P = 0.37$). In the present study, the total volume of RBC units transfused among SSRI users was higher compared with nonusers (adjusted difference of 0.9 units RBC). The discrepancy in terms of volume of RBC transfused between the 2 studies likely reflects methodological limitations with respect to large retrospective database studies in general. Due to sample size limitations, we are unable to explore this finding in greater detail. It is important that future studies examine individual SSRI medications, dosages, and duration of treatment prior to surgery.

It is noteworthy that studies in other clinical populations have observed excess bleeding with SSRIs. While this may reflect the inherent confounding associated with small observational analyses there may also be medical or pathophysiological explanations. For example, in orthopedic surgery patients in whom excess upper gastrointestinal bleeding was observed, concomitant administration of nonsteroidal anti-inflammatory drugs resulting in ulcerative lesions in the upper gastrointestinal tract could predispose to bleeding in the setting of SSRI-related antiplatelet effects.[17] On the other hand, patients with ischemic heart disease are more likely to be treated with other antiplatelet medications. Since other antiplatelet medications already contribute to bleeding risks, the incremental bleeding risks

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20621

Table 2. Unadjusted Postoperative Bleeding Outcomes

Clinical Outcomes	No SSRI Number of Events/Total Exposed (%)	SSRI Number of Events/Tota Exposed (%)	*P* Value
Primary and Key Secondary			
Reoperation for bleeding	119/4548 (2.6%)	8/246 (3.3%)	0.56
Postoperative RBC transfusion	3103/4548 (68.2%)	174/246 (70.7%)	0.41
Volume transfused (unit)[a]	4.0 (2.0, 6.0)	5.0 (3.0, 7.0)	<0.001
Composite of reoperation for bleeding, hematocrit drop ≥ 15%, or RBC transfusion	4157 (91.4%)	230 (93.5%)	0.25
Other Measures of Bleeding			
Hematocrit drop ≥ 15%	3173/3902 (81.3%)	185/231 (80.1%)	0.64
Hematocrit drop ≥ 30%	1986/4133 (48.1%)	100/231 (43.3)	0.14
%change in hematocrit from baseline	29.6% (19.1, 37.2%)	28.1% (18.2, 35.7%)	0.13
48-hour chest tube output (mL)[a]	600 (0, 1030)	563 (0, 975)	0.63
Other Blood Products (Total In-hospital)			
Any blood product transfusion	3191/4548 (70.2%)	176/246 (71.5%)	0.64
Platelet transfusion	1328/4548 (29.0%)	72/246 (29.0%)	0.98
FFP transfusion	1501/4548 (33.0%)	91/246 (37.0%)	0.20
Plasma transfusion	10/4548 (0%)	2/246 (1.0%)	0.12

Abbreviations: FFP, Fresh Frozen Plasma RBC, red blood cell; SSRI, selective serotonin reuptake inhibitor.
[a] Values reflect median (25th and 75th percentiles).

Table 3. Adjusted Comparisons of Primary and Key Secondary Bleeding Outcomes Between SSRI and No SSRI Use Groups

	OR (95% CI)	Wald χ^2	*P* Value
Reoperation for bleeding complications	1.14 (0.52–2.47)	0.102	.75
Any RBC transfusion	1.04 (0.75–1.44)	0.06	.81
Composite end point[a]	1.21 (0.67–2.19)	0.39	.53

Abbreviations: CI, confidence interval; OR, odds ratio; RBC, red blood cell; SSRI, selective serotonin reuptake inhibitor.
[a] Reoperation for bleeding, RBC transfusion, or drop in hematocrit ≥ 15%.

from SSRI, if present, may no longer be detectable as an additional risk. In another study of women who were taking SSRIs prior to delivery, SSRI use did not show any evidence of increased postpartum hemorrhage.[23] Therefore, the increase operative risk of SSRI in surgical patients has not been demonstrated beyond orthopedic patients.[17]

The strength of our study includes the large sample size of nearly 5000 CABG patients and prospective collection of clinical data and outcomes. The use of inpatient medication administration records ensured that SSRIs were indeed taken prior to CABG. This study represents the experiences at a single tertiary medical center and may not be applicable to use of SSRIs or outcomes of CABG procedures performed at all hospitals. The observational nature of our work has inherent limitations related to potential unmeasured confounders, such as the decision to prescribe SSRIs, doses of SSRIs, and the duration of usage, in association with bleeding outcomes. Further, the findings from this study pertain to SSRI as a class and do not provide data about individual SSRI antidepressants.

In conclusion, we did not find any evidence of an association between major bleeding events among patients undergoing CABG and the use of SSRIs. Although a higher volume of RBC units was transfused among SSRI-treated patients, this finding requires further research and does not appear to have significant clinical adverse effects.

References

1. Blumenthal JA, Lett HS, Babyak MA, et al; NORG Investigators. Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet*. 2003;362:604–609.

2. Pignay-Demaria V, Lesperance F, Demaria RG, et al. Depression and anxiety and outcomes of coronary artery bypass surgery. *Ann Thorac Surg*. 2003;75:314–321.
3. Ziegelstein RC, Meuchel J, Kim TJ, et al. Selective serotonin reuptake inhibitor use by patients with acute coronary syndromes. *Am J Med*. 2007;120:525–530.
4. Xiong GL, Jiang W, Clare R, et al. Prognosis of patients taking selective serotonin reuptake inhibitors prior to coronary artery bypass grafting. *Am J Cardiol*. 2006;98(1):42–47.
5. Cooper TA, Valcour VG, Gibbons RB, et al. Spontaneous ecchymoses due to paroxetine administration. *Am J Med*. 1998;104:197–198.
6. Serebruany VL, Glassman AH, Malinin AI; SADHART Study Group. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events. *Circulation*. 2003;108:939–944.
7. Serebruany VL, Suckow RF, Cooper TB, et al. Relationship between release of platelet/endothelial biomarkers and plasma levels of sertraline and N-desmethylsertraline in acute coronary syndrome patients receiving SSRI treatment for depression. *Am J Psychiatry*. 2005;162:1165–1170.
8. De Abajo FJ, Rodriguez LAG, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ*. 1999;319:1106–1109.
9. Dalton SO, Johanse C, Mellemkjaer L, et al. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding. *Arch Intern Med*. 2003;163:59–64.
10. Meijer WE, Heerdink ER, Nolen WA, et al. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. *Arch.Intern.Med*. 2004;164:2367–2370.
11. van Walraven C, Mamdani MM, Wells PS, et al. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ*. 2001;323:655–658.
12. Serebruany VL. Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? *Am J Med*. 2006;119:113–116.
13. Dent LA, Orrock MW. Warfarin-fluoxetine and diazepam-fluoxetine interaction. *Pharmacotherapy*. 1997;17:170–172.
14. De Maistre E, Allart C, Lecompte T, et al. Severe bleeding associated with use of low molecular weight heparin and selective serotonin reuptake inhibitors. *Am J Med*. 2002;113:530–532.
15. Movig K, Janssen M, Malefijt J, et al. Relationship of serotonergic antidepressants and need for bleed transfusion in orthopedic surgical patients. *Arch Intern Med*. 2003;163:2354–2358.
16. Andreasen JJ, Riis A, Hjortdal VE, et al. Effect of selective serotonin reuptade inhibitors on requirement for allogeneic red blood cell transfussion following coronary artery bypass surgery. *Am J Cardiovasc Drugs*. 2006;6(4):243–250.
17. Lichtman JH, Bigger JT, Blumenthal JA, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment. A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research. *Circulation*. 2008;118:1768–1775.
18. Thombs BD, de Jonge P, Coyne JC, et al. Depression screening and patient outcomes in cardiovascular care: a systematic review. *JAMA*. 2008;300(18):2161–2171.
19. Harris PJ, Harrel FE, Lee KL, Behar VS, Rosati RA. Survival in medically treated coronary artery disease. *Circulation*. 1979;60:1259–1269.
20. Tatsumi M, Groshan K, Blakely RD, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur J Pharmacol*. 1997;340:249–258.
21. Kim J H-J, Newby LK, Clare RM, et al. Clopidogrel use and bleeding after coronary artery bypass graft surgery. *Am Heart J*. 2008;156(5):886–892.
22. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med*. 1997;127:757–763.
23. Salkeld E, Ferris LE, Juurlink DN. The risk of postpartum hemorrhage with selective serotonin reuptake inhibitors and other antidepressants. *J Clin Psychopharmacol*. 2008;28(2):230–234.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20621