

Use of Serotonergic Antidepressants and Bleeding Risk in Orthopedic Patients

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ABSTRACT

Background: Selective serotonin reuptake inhibitors have been associated with an increased bleeding tendency. Information on the impact of a possible impaired hemostasis associated with the perioperative use of selective serotonin reuptake inhibitors is limited. This study aimed to determine the association between the perioperative use of selective serotonin reuptake inhibitors and the amount of blood loss during surgery and perioperative transfusion requirements.

Methods: The authors conducted a retrospective cohort study among patients who underwent elective primary total hip arthroplasty in two hospitals from the period of July 1, 2004 until July 1, 2008. The index group included all users of both serotonergic and nonserotonergic antidepressants. The reference group included a random sample (ratio 1:3) of nonusers. The primary outcome was the amount of intraoperative blood loss. The requirement for blood transfusion was a secondary outcome. The outcomes were adjusted for confounding factors (comorbidity and comedication) using regression techniques.

Results: The index group included 66 users of serotonergic and 29 users of nonserotonergic antidepressants, and the reference group included 285 patients. After adjustment for confounding factors, mean blood loss during surgery was significantly higher in the users of selective serotonin reuptake inhibitors when compared with the reference group: 95 ml (95% CI 9–181). Mean blood loss in the users of nonserotonergic antidepressants did not differ from the reference group. Users of antidepressants did not have a higher risk for transfusion.

Conclusions: Patients undergoing total hip arthroplasty who continue the use of serotonergic antidepressants show a significantly higher, but clinically unimportant, intraoperative blood loss, without an increase in perioperative transfusion requirements.

What We Already Know about This Topic

- ❖ Selective serotonin reuptake inhibitors (SSRIs) have been associated with an increased bleeding tendency, although the clinical relevance of this to perioperative care is uncertain

What This Article Tells Us That Is New

- ❖ In a retrospective review of patients undergoing total hip arthroplasty (66 on SSRIs and a control cohort of 285), mean blood loss was slightly greater (95 ml) in patients on SSRIs, although this was not associated with increased incidence or amount of transfusion

DURING the last two decades, the use of antidepressant agents has increased substantially, and selective serotonin reuptake inhibitors (SSRIs) have gradually substituted the classic tricyclic agents as drugs of first choice. These antidepressants are particularly popular because of their lower toxicity and better tolerability.^{1,2} The use of antidepressant agents with serotonergic activity has been associated with an increased bleeding tendency.³⁻⁷ Because serotonin within the platelets promotes platelet aggregation, depletion of serotonin from platelets resulting from inhibition of serotonin reuptake by SSRIs is most likely the underlying mechanism of impaired hemostasis.⁸⁻¹¹ The relative frequency of SSRI-related bleedings seems to be proportionate to the degree of serotonin reuptake inhibition.¹²

Several observational studies on the use of SSRIs and bleeding risk have been published,^{3-7,12-19} but only two studies concentrated on the use of SSRIs and bleeding risk during the perioperative period.^{13,18} An increased volume of blood loss and the subsequent need for blood transfusion during orthopedic surgery was found in patients using SSRIs.¹⁸ However, preoperative use of SSRIs was not associated with increased requirement for erythrocyte transfusion among patients undergoing coronary artery bypass grafting.¹³ These results are contradictory about the impact of a possible impaired hemostasis associated with the perioperative use of SSRIs. Hence, with this limited

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information, the safety of SSRIs concerning perioperative bleeding risk is still an important clinical concern.

Although anesthesiologists have to consider the risks of impaired hemostasis and the resulting increased bleeding in patients using SSRIs, there is little evidence on the perioperative management of these drugs, that is, to continue or to withhold them.^{20–22} This multicenter study among orthopedic patients undergoing primary total hip arthroplasty aimed to determine the association between the perioperative use of SSRIs and the amount of blood loss during surgery and perioperative transfusion requirements.

Materials and Methods

Patients

This retrospective observational cohort study was conducted in two Dutch hospitals: the University Medical Center Utrecht, Utrecht, The Netherlands, and the Medical Center Alkmaar, Alkmaar, The Netherlands, a general teaching hospital. The study protocol was approved by the Medical Ethics Board of both hospitals. Because the study only documented routinely gathered patient data, the ethics boards waived the need for written informed consent. Patients who underwent elective primary total hip arthroplasty from the period of July 1, 2004, until July 1, 2008, were eligible to enter the study. These patients were identified by means of hospital administrative databases containing information on orthopedic procedures performed within the study period. Patients were excluded from the study if they were younger than 18 yr, had a preexisting bleeding disorder, underwent additional surgical procedures, or if their medical records were missing.

After the indication for total hip arthroplasty was set by the orthopedic surgeon, all patients visited the anesthesiologist at the outpatient preanesthesia evaluation clinic. Perioperative care, including type of prosthetic (cemented or noncemented), type of anesthesia (spinal or general), or additional investigations was left at the discretion of the attending physicians.

Antidepressant Agents

The index group consisted of users of antidepressant agents. A user of an antidepressant agent was defined as a patient using an antidepressant agent on the day of outpatient preanesthesia evaluation and who was still using this antidepressant on the day of hospital admission. The minimum duration of the treatment period with antidepressants before hospital admission was 2 weeks.¹⁰ Patients using antidepressants for less than 2 weeks were excluded. In case patients were admitted within 2 weeks after they visited the outpatient preanesthesia clinic, the community pharmacy was contacted to obtain the date of first prescription.

For the current study, a difference was made between the use of serotonergic and nonserotonergic antidepressants based on their affinity for the serotonin (5-hydroxytryptamine) reuptake transporter.²³ The first group, showing high affinity for the serotonin reuptake transporter, included sertraline, fluvoxamine, escitalopram, paroxetine, venlafaxine,

fluoxetine, citalopram, duloxetine, and clomipramine. The second group, with low or none affinity, included imipramine, doxepin, amitriptyline, nortriptyline, maprotiline, mianserin, mirtazapine, trazodone, and bupropion.

The reference group (nonusers of antidepressant agents) was matched to the index group on center and month of surgery in a one-to-three ratio with the index group. Subjects were randomly sampled from all patients who had their surgery within a range of 2 weeks before or 2 weeks after the day of surgery of the index patient. If a reference patient met the exclusion criteria, another suitable patient was selected in the same manner. Data on perioperative use of antidepressants were derived from (electronic) medical records and hospital pharmacy databases containing information on medication prescription during hospital admission.

Outcomes

The primary outcome was the amount of intraoperative blood loss (milliliter). This volume was routinely estimated by the anesthesiologist at the end of surgery and documented in the medical file of the patient. The requirement for blood transfusion (units of red blood cells and fresh frozen plasma) during surgery and in the postoperative period (during admission) was used as a secondary outcome variable. The number of units of blood products administered was obtained from the hospital transfusion laboratory. The unique patient identification number together with the surgery date was used to merge databases.

Potential Confounders

The (electronic) medical records of the index and reference group were assessed for potential confounding variables, including patient and surgery characteristics, that is, age, gender, weight and height, smoking status, alcohol abuse, preoperative and postoperative hemoglobin levels, comorbidity, comedication, duration of surgery, type of prosthetic (cemented or noncemented), and type of anesthesia (spinal or general).

Statistical Analysis

On the basis of previous studies, we assumed an intraoperative blood loss of 550 ml (SD 340 ml) to be representative for an average total hip arthroplasty.^{24–26} Sample size calculation was based on the hypothesis that a relative increase in blood loss with 25% or more (690 ml or more) among users of SSRIs would be clinically relevant. Given a one-to-three ratio of index to control group and using a two-sided alpha of 0.05 with a power of 0.80, a number of 60 patients was required in the index group and a number of 215 patients in the control group.

Baseline characteristics of all patients were described as proportions or means \pm SD as appropriate. Univariate analyses were performed using the chi-square test or Fisher exact test where appropriate. Student independent sample *t* tests were used for two-group comparison when the data satisfied assumptions for parametric analysis and Mann-Whitney U tests when the data did not satisfy assumptions for parametric analysis.

Multivariable linear regression analysis was used to adjust the association between use of antidepressants and intraop-

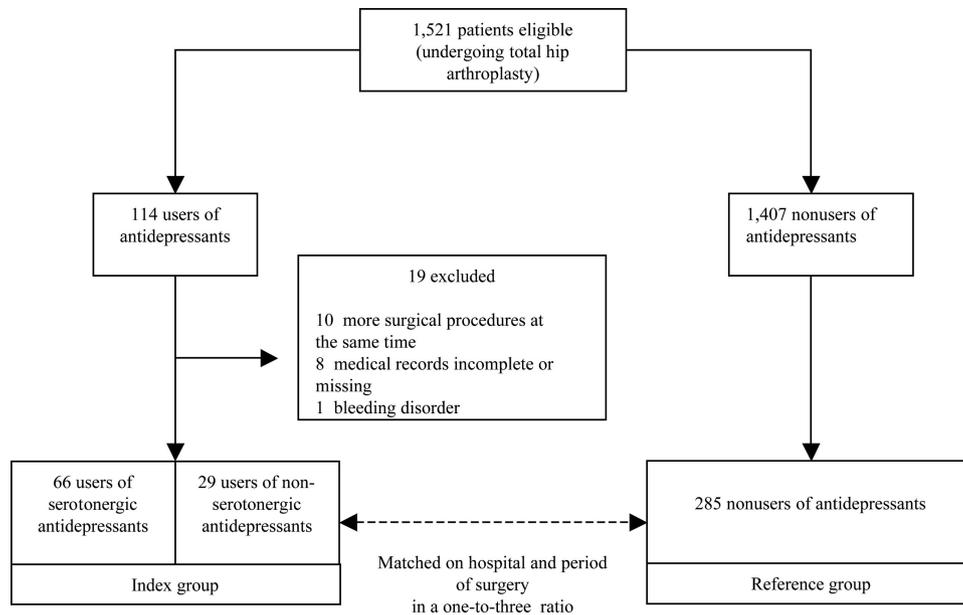


Fig. 1. Patient flowchart.

erative blood loss for confounding factors in two ways. First, a classic regression analysis was performed including both the determinant (use of SSRI) and confounders. In addition, in a second regression model, the individual probabilities for use of an SSRI were calculated (propensity score) and included as a confounding factor. The propensity score for use of an SSRI was derived from a multivariable logistic regression model including all variables that were significantly related to the use of an SSRI in univariable analysis.

Multivariable logistic regression analysis was used to adjust the association between the use of antidepressants and transfusion. In the multivariate regression models, a potential confounding factor was included if its *P* value was ≤ 0.2 in univariate analysis or when it changed the estimate of the effect by more than 10%.²⁷ The associations between the determinant and the outcomes of interest were expressed as mean differences or odds ratios with 95% CI. SPSS release 14.0 (SPSS Inc., Chicago, IL) was used for statistical analysis.

Results

During the study period, a total of 1,654 elective primary total hip arthroplasty were performed in 1,521 patients. Within this group, 114 users of any antidepressant were identified (7.5%). Eighty patients (5.3%) used a serotonergic antidepressant and 34 patients (2.2%) a nonserotonergic antidepressant. Nineteen of the 114 patients were excluded: 10 patients underwent more surgical procedures at the same time; in 8 patients, medical records were incomplete or missing; and 1 patient had a bleeding disorder. The remaining 95 patients were included in the index group: 66 users of a serotonergic antidepressant and 29 users of a nonserotonergic antidepressant (fig. 1). In the serotonergic group, 33 patients (50%) used paroxetine, 12 (18%) used citalopram, and 11 (17%) were on venlafaxine. The remaining 10 (15%)

patients were on different other SSRIs. In the nonserotonergic group, 19 patients (66%) used amitriptyline, 4 (17%) were on mirtazapine, 4 (13%) on trazodone, and 2 were on other nonserotonergic antidepressants. The reference group included 285 patients. Patients matched to the users of a serotonergic antidepressant showed no clinically important differences to those matched to the users of nonserotonergic antidepressants and were, therefore, combined to form one reference group of nonusers. Table 1 summarizes the general characteristics of the study patients. Mean age of the users of antidepressants and nonusers was 67 and 68 yr, respectively.

Table 2 shows the amount of intraoperative blood loss. Mean blood loss during surgery was significantly higher in the group of users of SSRIs when compared with the reference group (difference of 106 ml, 95% CI 22–191). Adjustment for confounding factors using a classic regression analysis revealed a difference of 95 ml (95% CI 9–181). The propensity score predicting the probability of a patient using an SSRI was calculated. Factors significantly related to use of an SSRI were smoking, use of nonsteroidal antiinflammatory drugs, use of methotrexate, and coronary artery disease. The area under the receiver operator characteristic curve of the propensity model was 0.70 (95% CI 0.63–0.76). The additional regression analysis including the propensity score as a confounding factor showed results comparable with the initial analysis: mean blood loss during surgery was significantly higher in users of SSRIs when compared with the reference group (difference of 99 ml, 95% CI 12–186). Mean blood loss in the patients using nonserotonergic antidepressants did not significantly differ from the reference group (difference of –96 ml, 95% CI –209 to 17).

Table 3 shows the proportion of patients with an erythrocyte transfusion and the mean number of erythrocyte units

Table 1. General Characteristics of Study Patients

	Antidepressants				Nonusers (n = 285)
	Serotonergic (n = 66)	P value*	Non-serotonergic (n = 29)	P Value*	
University hospital	18 (27)	0.40	13 (45)	0.19	93 (33)
Male gender	15 (23)	0.12	5 (17)	0.09	93 (33)
Mean weight (kg)	73 ± 14	0.06	78 ± 15	0.50	76 ± 14
Mean height (cm)	167 ± 7	0.01	169 ± 6	0.44	170 ± 9
Mean age (yr)	67 ± 12	0.73	67 ± 13	0.53	68 ± 11
Smoking	20 (32)	0.10	5 (17)	0.55	61 (22)
Mean preoperative hemoglobin level (mm†)	8.5 ± 0.8	0.68	8.1 ± 0.9	0.01	8.6 ± 0.7
Mean duration of surgery (min)	97 ± 48	0.49	115 ± 45	0.06	99 ± 44
Mean duration of postoperative period (d)	9.2 ± 8.9	0.01	8.2 ± 6.2	0.27	6.7 ± 5.4
Cemented prosthetics	40 (61)	0.36	20 (69)	0.19	146 (51)
Spinal anesthesia	41 (62)	0.35	16 (55)	0.21	201 (71)
Comedication					
Erythropoietin	8 (12)	0.97	9 (31)	0.01	35 (12)
NSAIDs	9 (14)	0.01	3 (10)	0.18	13 (5)
COX-2 inhibitors	2 (3)	0.68	0 (0)	1.00	7 (3)
Antiplatelet drugs	1 (2)	1.00	0 (0)	1.00	7 (3)
Heparine	0 (0)	0.60	0 (0)	1.00	6 (2)
Calcium antagonists	7 (11)	0.71	3 (10)	0.74	26 (9)
Corticosteroids	3 (5)	0.44	1 (3)	0.59	8 (3)
Iron supplements	6 (9)	0.44	6 (21)	0.02	19 (7)
Methotrexate	3 (5)	0.08	0 (0)	1.00	3 (1)
Diuretics	13 (20)	0.89	12 (41)	0.01	58 (20)
Comorbidity					
Diabetes mellitus	6 (9)	0.73	6 (21)	0.12	30 (11)
Heart failure	1 (2)	1.00	0 (0)	1.00	5 (2)
Hypertension	21 (32)	0.18	12 (41)	0.94	116 (41)
Renal disease	1 (2)	0.47	0 (0)	1.00	2 (1)
Cancer	1 (2)	1.00	1 (3)	0.39	4 (1)
Coronary artery disease	1 (2)	0.06	2 (7)	1.00	23 (8)

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

* Compared with nonusers.

COX2 = cyclooxygenase-2; NSAIDs = nonsteroidal antiinflammatory drugs.

per transfused patient. There were no significant differences between users of antidepressants and the reference group. After adjustment for confounding, users of antidepressants did not have a higher risk for transfusion compared with the reference group (users of serotonergic antidepressants: odds ratio 1.5 [95% CI 0.7–3.3] and users of nonserotonergic antidepressants: odds ratio 1.4 [95% CI 0.5–4.1]). One patient in the reference group underwent a transfusion with fresh frozen plasma.

Discussion

Patients undergoing primary total hip arthroplasty who continued the use of SSRIs showed a significantly increased amount of blood loss of 100 ml on average during surgery. This increased blood loss did not increase perioperative transfusion requirements. We did not find an association between the amount of intraoperative blood loss and the use of nonserotonergic antidepressants.

Table 2. Unadjusted Means, Adjusted Means, and Mean Differences in Intraoperative Blood Loss for Patients Using Serotonergic or Nonserotonergic Antidepressants

	Unadjusted Blood Loss, ml (95% CI)	Difference in Blood Loss (ml) Compared with Nonuse* (95% CI)	Adjusted Blood Loss, ml (95% CI)	Difference in Blood Loss (ml) Compared with Nonuse* (95% CI)
Serotonergic	672 (582 to 762)	106 (22 to 191)	661 (575 to 747)†	95 (9 to 181)†
Nonserotonergic	539 (461 to 617)	−27 (−140 to 86)	470 (357 to 583)‡	−96 (−209 to 17)‡

* Intraoperative blood loss in the reference group was 566 mL (95% confidence interval [CI] 530–601). † Adjusted for weight, height, preoperative hemoglobin level, nonsteroidal antiinflammatory drugs, iron supplement, coronary artery disease, type of prosthetics, type of anesthesia, and duration of surgery. ‡ Adjusted for sex, weight, preoperative hemoglobin level, erythropoietin, iron supplement, diabetes mellitus, renal disease, cancer, coronary artery disease, duration of surgery, type of prosthetics, and type of anesthesia.

Table 3. Proportion of Patients with a Red Blood Cell Transfusion and Mean Number of Transfused Units per Patient for Patients Using Serotonergic or Nonserotonergic Antidepressants

	Proportion of Patients Transfused (%)	Mean Number of Red Blood Cell Units/Transfused Patient (95% CI)
Nonusers	54/285 (19)	2.8 (2.0–3.7)
Serotonergic	17/66 (26)	2.4 (1.8–2.9)
Nonserotonergic	9/29 (31)	2.2 (1.6–2.9)

CI = confidence interval.

Our results confirm the previously reported association between perioperative use of SSRIs and intraoperative blood loss, although the effect on the amount of blood loss in the current study is less severe.¹⁸ Movig *et al.* reported a 75% increased volume of intraoperative blood loss in orthopedic patients using SSRIs, whereas we found only a modest increase of 17%. The choice of study population and confounding variables could have contributed to the difference in results. We included orthopedic patients undergoing elective primary total hip arthroplasty. In the study of Movig *et al.*, the study population consisted of patients who received hip, knee, or spine implants. Because Movig *et al.* did not report concomitant diseases and medication of users of antidepressants, we could not compare these variables with our data. We did not find a significant increase in blood transfusion requirement as found by Movig *et al.*¹⁸ Our results are consistent with the findings of Andreasen *et al.*¹³ who found no substantially increased need for transfusion in patients undergoing coronary artery bypass grafting while using SSRIs.

The underlying mechanism for the increased risk in bleeding by SSRIs may occur *via* a decrease in intraplatelet serotonin concentrations affecting platelet aggregation.¹¹ Surgical procedures itself have been associated with decreased platelet serotonin and a concurrent increase in plasma serotonin.²⁸ The combination of both effects may act synergistically, resulting in impaired hemostasis and consequently a higher bleeding risk in surgical patients using SSRIs.

The classification of antidepressants used in previous studies on bleeding risk has been a matter of debate. We used the classification based on the binding properties of most common transporter and receptor sites.²³ This recently published model identifies antidepressants based on their pharmacologic binding properties and divides them into four clusters. The model is useful in the understanding of the adverse drug reaction profile of antidepressants. The first cluster includes antidepressants with high affinity for the serotonin reuptake transporter. The other clusters include antidepressants with low or no affinity.

We deliberately chose to study the effects of SSRIs on intraoperative blood loss in a highly standardized elective surgical procedure in a well-defined population, such as total hip arthroplasty. Furthermore, we collected many other fac-

tors that may potentially influence the amount of intraoperative blood loss, such as duration of surgery, type of anesthesia, and comedication. This allowed us to perform adjustments for confounding factors in the analysis.

Still, some potential limitations of our study have to be addressed. First, this study was a retrospective nonrandomized observational study. To prevent selection bias, we selected all users of antidepressants and a random sample of control subjects from a well-defined population without knowledge of outcome parameters at the time of selection. Furthermore, to increase generalizability of the results, we included patients from two different hospitals. Second, the estimated volume of intraoperative blood loss by the anesthesiologist was reasonably inaccurate. However, this inaccuracy likely was a random or nondifferential misclassification; because by the time blood loss was estimated, the anesthesiologists were not aware of the study. Moreover, anesthesiologists likely did not selectively report blood loss because, in daily clinical practice, bleeding is not thought to be associated with antidepressants. SSRIs are not mentioned in any anesthetic or orthopedic protocol as a potential risk for impaired hemostasis and increased perioperative bleeding. Furthermore, we also determined transfusion requirements. The documentation of blood transfusion is a highly accurate standardized procedure in each hospital. It should be noted, however, that transfusion requirements do not necessarily correlate with intraoperative blood loss. Transfusions of red blood cells are usually based on more variables than the amount of bleeding, including hemoglobin values and the existence of comorbidity. We collected information on these potential covariates and adjusted for them in statistical analysis. In recent years, a lower hemoglobin level probably may have been acceptable for an individual patient. However, as we matched patients from the reference group to the index group on month of surgery, the proportion of patients in the index and reference group in a certain year is the same. Therefore, the possible influence of acceptance of a lower hemoglobin level on the decision for transfusion would have been nondifferential for the different groups. Third, there is some evidence that depression itself might be associated with alterations in platelet reactivity, which might potentially lead to confounding by indication. Although many studies have found that patients with depression have exaggerated platelet activation, quite a number of others show no such relationship or even lower levels of platelet activation in patients with depression.²⁹ Larger studies with standardized methods of assessing platelet function are needed to resolve this question. Therefore, the possible influence of depression on bleeding risk remains unclear. Furthermore, antidepressants are prescribed for numerous other indications such as anxiety and panic disorders and in only 50% for depression.³⁰ As mentioned earlier, we believe that confounding by indication was not an important issue, especially as we did not find a significant difference in blood loss between users of nonserotonergic antidepressants and the reference group.

Perioperative continuation of SSRIs is associated with increased blood loss. Because of the widespread and still increasing use of SSRIs, a relatively large number of surgical patients may be exposed to this potential risk. However, in contrast with a previously reported severe increase in the amount of blood loss in orthopedic patients using SSRIs, we found only a moderate increase (17%). Although the literature remains conflicting, the clinical impact of SSRI use on bleeding in total hip arthroplasty seems limited. When the risk of increased blood loss is weighted against the risks associated with discontinuing ongoing treatment with SSRIs, it seems reasonable not to advocate discontinuation of SSRIs before total hip arthroplasty in otherwise healthy patients. However, anesthesiologists should consider the increased risk of bleeding in combination with other patient or surgery factors, such as the use of antiplatelet drugs such as clopidogrel or nonsteroidal antiinflammatory drugs, preexisting bleeding disorders, or intracranial surgery.

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