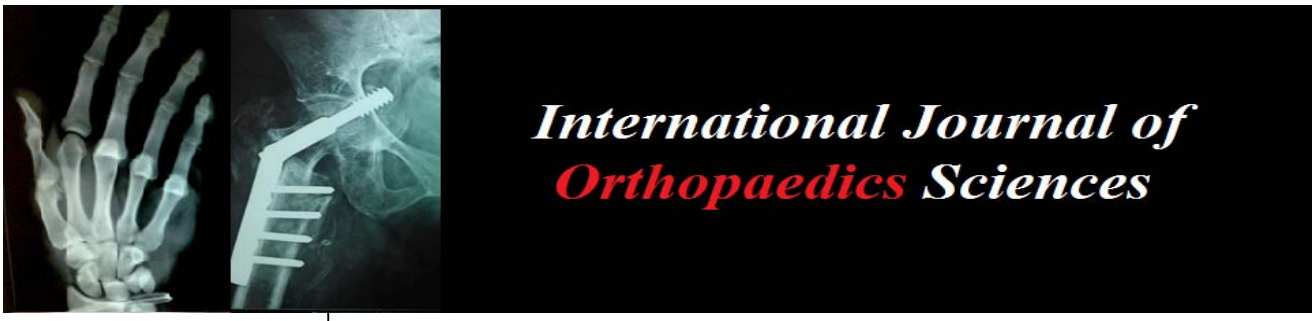

ISSN: 2395-1958
IJOS 2015; 1(3): 01-05

www.orthopaper.com
Received: 15-06-2015
Accepted: 16-07-2015

Mary R. Thottam
Department of Veterans Affairs, North Texas, Anesthesiology and Pain Management Services

Peggy Mancuso
Texas Woman's University 5500 Southwestern Medical Avenue, Dallas, TX 75235-7299

Dr. Enas Kandil
5323 Harry Hines Blvd
Dallas, Texas-75390

Correspondence
Mary R. Thottam
Department of Veterans Affairs, North Texas, Anesthesiology and Pain Management Services

Serotonergic antidepressants and perioperative bleeding risk in patients undergoing total knee arthroplasty: A retrospective study

Mary R. Thottam, Peggy Mancuso, Enas Kandil

Abstract
Background: Serotonergic antidepressants inhibit platelet aggregation, and use of these drugs has been associated with adverse bleeding events. The objective of this study was to determine the association of preoperative use of serotonergic antidepressants and perioperative bleeding in patients undergoing total knee arthroplasty.
Methods: A retrospective analysis was conducted of 80 patients who underwent elective primary total knee arthroplasty in a large hospital. The index group included 40 patients who used serotonergic antidepressants in the preceding 4 weeks prior to surgery, and the reference group included 40 patients who were nonusers. The primary outcome was the change in hematocrit; and the secondary outcomes were the amount of estimated blood loss and the requirement for blood transfusion.
Results: Comparing the patients who were using SSRIs and those who were not, no statistically significant difference was observed in the level of the three dependent variables of Hct change, estimated blood loss and transfusion units ($p > .05$). The effect of the use of SSRI on preoperative hemoglobin and hematocrit levels, however, was significant ($p = .027$; $p = .023$, respectively), as patients who used SSRI had significantly lower levels of preoperative hemoglobin and preoperative hematocrit.
Conclusions: This study concluded that patients undergoing total knee arthroplasty who continued to use serotonergic antidepressants did not show a statistically significant perioperative blood loss based on the three outcome measures of change in hematocrit, blood transfusion needs, and estimated blood loss.

Keywords: Serotonergic Antidepressants, Perioperative Bleeding Risk, Patients, Knee Arthroplasty

1. Introduction
Serotonergic antidepressants such as the selective serotonin reuptake inhibitors (SSRI) are one of the most extensively prescribed and the first-choice pharmacological agents used for the treatment of depression, obsessive-compulsive disorder, anxiety disorders, and a variety of psychiatric disorders [1, 2]. Although known to be safe, several case reports and observational studies noted significant associations between serotonergic antidepressant use and abnormal bleeding events such as ecchymoses, hematoma, purpura, epistaxis, vaginal bleeding, upper gastrointestinal bleeding, intracranial bleeding, and perioperative bleeding [3, 4].
Clinical reports of increased risk of abnormal bleeding in patients using these drugs emerged soon after the introduction of this class of agents in the 1990s [5]. Reported bleeding events following initiation of SSRI therapy included spontaneous bleeding events such as ecchymoses, purpura, epistaxis, and vaginal bleeding [5, 6]. Several observational studies also indicated increased risk for upper gastrointestinal hemorrhage in patients on SSRI therapy. One of the first observational studies was a nested case-control study in 1999 by de Abajo, Rodriguez, & Montero [7], which noted a three times increased risk for upper gastrointestinal bleeding. Since then, several other studies have reported an association between SSRI use and spontaneous upper gastrointestinal hemorrhage [8]. A case-control study by Meijer *et al.*, [4] observed a 2.6 fold increased risk of gastrointestinal bleeding events in patients receiving SSRI medications and the findings of this study were similar to the initial 1999 report of de Abajo *et al.* [7]
Platelet aggregation is essential for hemostatic thrombus formation, and this process requires the release of serotonin from the platelets [1, 9]. Serotonin, is a neurotransmitter hormone (5-hydroxytryptamine, 5-HT), which is primarily stored in the blood platelets (99%), in the enterochromaffin cells of the intestines, and the neurons in the central nervous system [1, 9, 10].

In several human studies, continued uses of serotonergic antidepressants have been shown to deplete platelet serotonin content by 80-90% [2]. Serotonergic drugs block serotonin reuptake into thrombocytes, depleting platelet serotonin stores, thus reducing platelet aggregation [11, 12]. This pharmacological mechanism of anti-platelet properties of serotonergic drugs is postulated to affect primary hemostasis, potentiating hemorrhagic events.

The inhibition of platelet aggregation caused by the serotonergics suggests that these drugs may increase the risk of perioperative and post-surgical bleeding [13, 14]. Nevertheless, few studies have researched the proposed relationship between the uses of serotonergic antidepressant medications and increased surgical bleeding, and data on this association thus far is inconclusive and conflicting. A study by Movig *et al.* in (2003) concluded that SSRI use in patients undergoing orthopedic surgery is associated with a 3.7 fold increased risk of bleeding and subsequent necessity for blood transfusions [4]. Similar results were presented in a study of patients undergoing spinal surgery, by Sayadipour *et al.* in 2012, [15] which found a statistically significant higher blood loss in those taking serotonergic antidepressants compared to the control group. These researchers recommended that clinicians should consider tapering serotonergic antidepressants prior to elective surgery. Gartner *et al.* (2010) [13] conducted a population based cohort study on patients who underwent breast surgery with a conclusion that current use of SSRIs was associated with increased risk of re-operation due to post surgical bleeding. In contrast, Andreasen *et al.* in 2006 [16], reported that preoperative SSRI use was not associated with any substantially increased need for red blood cell transfusion among patients undergoing coronary artery graft bypass surgery. Because the prevalence of SSRI use is increasing, the serotonergic effects of these drugs can pose a potential risk for increased surgical bleeding resulting in increased perioperative morbidity and mortality. Clinicians should, therefore, be aware of the associated potential bleeding risk with SSRI use during the preoperative period. Although preoperative medication management is a vital component of perioperative care, there are no evidence-based guidelines for the perioperative management of patients on serotonergic antidepressants prior to elective surgery [17]. In light of conflicting evidence there is, thus, the necessity to further investigate the association of serotonergic antidepressant use and excessive perioperative bleeding. Evidence is needed to determine if the risk of SSRI-associated bleeding in perioperative situations is greater than the benefit provided by the antidepressant benefits of these drugs. A summary of the findings from the various studies are presented in Table 1.

Table 1: *Literature Analysis*

Authors(Year)	Study Population	Study Design	Results
Movig *et al.* (2003)	Orthopedic patients undergoing surgery in 1999-2000	Retrospective cohort	Risk of blood transfusion quadrupled in serotonergic antidepressant users
Gartner *et al.* (2010)	Comparison of post-surgical bleeding risk in SSRI users versus non users found that current use of SSRI increased the risk of re-operation after breast surgery (n=14,464)	Population based cohort study	Current use of SSRI increased the risk of re-operation after breast surgery due to post operative bleeding from 2.7% to 7%.
Sayadipour, *et al.* (2012)	1,539 patients who underwent elective spinal fusion	Retrospective case control study	Mean blood loss for the antidepressant group was 23% more than the control group of patients who were not taking serotonergic antidepressants
Richter, *et al.* (2011)	990 patients who underwent percutaneous gastrostomy	Retrospective cohort study	Serotonergic antidepressant use prior to the procedure was associated with a significantly higher odds of post procedure bleeding. (*OR* 4.1; 95% *CI*, [1.1-13.4]; *p* = .04)
Andreasen *et al.* (2006)	Patients undergoing coronary artery bypass graft (CABG)	Population based, prospective, controlled, cohort study	Preoperative use of SSRIs was not associated with any substantially increased requirement for red blood cell transfusion. Adjusted RR in SSRI users was 1.0 (95% *CI* [0.7, 1.4]).
Xiong *et al.* (2010)	Patients undergoing CABG between 1999 and 2003	Prospective, control study	Reoperation due to bleeding among SSRI users was not significantly different compared to the control group, however, the adjusted total volume of red blood cell units transfused was higher in the SSRI group.
van Haelst *et al.*, (2010)	Elective primary total hip arthroplasty in two hospitals from the period of July 1, 2004 until July 1, 2008	Retrospective cohort study	The mean blood loss during surgery was 100 ml more in the users of SSRIs when compared with the reference group.
(Salkeld, Ferris, & Juurlink, 2008)	2,460 postpartum hemorrhage cases and 23,943 matched controls in this study	Population based nested case control study	There was no significant association between use of serotonergic antidepressants and risk of post partum hemorrhage

2. Materials and Methods

2.1 Population and Sample

The target population chosen for this clinical inquiry project was veterans who have undergone primary, elective, unitary, total knee arthroplasty. A convenience sample was selected from the hospital electronic health record database. The index group of patients consisted of those patients who were taking serotonergic antidepressants, which included sertraline, fluoxetine, paroxetine, citaloprim, and venlafaxine, which have been described as having affinity for the serotonin reuptake inhibitors four weeks prior to the day of surgery. The control group included patients who did not use these specific

antidepressants in the preceding 4 weeks prior to the surgery. Patients with pre-existing coagulation disorders, platelet disorders, those younger than 18 years of age, and those undergoing additional procedures were excluded from the study. A G* Power 3. 1. 2. Analysis determined that a minimum of 64 cases would be sufficient to evaluate the outcomes. This clinical inquiry project evaluated a total of 80 patients; 40 who have used the specific serotonergic antidepressants (index group) in the four weeks prior to total knee arthroplasty surgery and 40 who have not used antidepressants (control group) in the four weeks prior to total knee arthroplasty surgery.

2.2 Method

This retrospective research study was conducted in a large Veterans Affairs Medical Center in Texas. After obtaining Instituitional Review Board approval of the hospital and the Texas Woman's University, patients were categorized into two groups: (a) the index group, which included patients who were using the specified serotonergic antidepressants in all available doses during the 4 weeks prior to surgery, and (b) the control group, which included patients undergoing total knee arthroplasty and not taking the specific antidepressants. Data were collected reviewing the computerized patient record system of patients who underwent total knee arthroplasty from December 2012 to January 2006 in reverse chronological order. A total of 200 charts were reviewed in order to obtain the required sample of 40 patients who were using serotonergic antidepressants and who met the inclusion criteria. Data on preoperative use of serotonergic antidepressants were retrieved from electronic medical records and the hospital pharmacy database containing information on medication prescriptions. Patients with pre-existing coagulation disorders, platelet disorders, those younger than 18 years of age, and those undergoing additional procedures were excluded from the study. It is the established policy at this hospital to evaluate all patients undergoing elective surgery to have a pre-anesthesia evaluation within 30 days of elective surgery, and this included preoperative medication management.

2.3 Data Analysis

Data were analyzed using the statistical software Statistical Package for the Social Sciences 19.0 (SPSS 19.0). Data were examined for outliers and missing data, and tests of assumption and normalcies were conducted on the collected data. Statistical procedures conducted included means and standard deviations, Pearson's product moment correlations, and multiple regression analyses. Descriptive statistics were calculated for all demographic, independent and dependent variables, and is shown in Table 2. Pearson's product moment correlations were performed between dependent variables and pre-operative hemoglobin and hematocrit and between the dependent variables of change in hematocrit, estimated blood loss, and blood transfusions. The three outcome measures of change in hematocrit, estimated blood loss, and blood transfusion needs were analyzed using three separate multiple regression analysis using SSRI group (user versus non-user) as the predictor variable; and change in hematocrit, number of blood transfusion units, and estimated blood loss as individual outcome variables.

Table 2: *Means and Standard Deviations of Demographic and Medical Variables*

	N	*Mean*	*Standard Deviation*	*Minimum*	*Maximum*
Age	80	63.15	7.97	46.0	83.0
Body Mass Index	80	30.14	4.89	18.19	43.90
Pre-operative Hemoglobin	80	14.05	1.38	14.05	17.30
Pre-operative Hematocrit	80	42.11	3.62	42.11	51.10
Platelets	80	229.38	68.0	229.38	481.00
Plasma Thromboplastin Time	80	12.96	.987	12.96	14.90
Prothrombin Time	80	29.41	2.994	29.41	36.00
Fluid Volume Infused	80	1352.35	524.47	400.00	3200.00
Tourniquet Time	80	109.58	18.70	56.00	154.00
Change in Hematocrit	80	12.06	3.57	4.20	20.10
Estimated Blood Loss	80	54.94	46.37	10.00	200.00
Transfusion Units	80	.41	1.03	.00	4.00

3. Results

As shown in Table 2, hematocrit change ranged from 4.2 to 20.1 with a mean of 12.06 (*SD* = 3.57), estimated blood loss ranged from 10 to 200 with a mean of 54.94 (*SD* = 46.37), and blood transfusion units ranged from 0 to 4 with a mean of .41 (*SD* = 1.03). The potential relationship between the use of serotonergic antidepressant usage and the demographic variables of age and body mass index were examined using the analysis of variance (ANOVA), showing that in both cases again, the relationship is not statistically significant (p = .824; p = .335, respectively). However, the effect of the use of SSRI on preoperative hemoglobin and hematocrit levels is significant (p = .027; p = .023, respectively), where patients who used SSRI had significantly lower levels of preoperative hemoglobin and preoperative hematocrit as shown in Table 3.

Table 3: *Effect of SSRI Use on Pre-Operative Hemoglobin and Hematocrit*

	N	*Mean*	*SD*	*F*	*P*
Pre-operative Hb				5.08	.027
SSRI Group	40	13.72[a]	1.40		
Non-SSRI Group	40	14.40[b]	1.31		
Pre-operative Hct				5.35	.023
SSRI Group	40	41.20[a]	3.43		
Non-SSRI Group	40	43.03[b]	3.62		

To analyze the three outcome measures, three separate multiple linear regressions were conducted using SSRI group (user versus non-user) as the predictor variable; and change in hematocrit, number of blood transfusion units, and estimated blood loss as individual outcome variables. The effect of SSRI usage on the three dependent variables is examined, the results of which are displayed in Table 4. Comparing the patients who were using SSRIs and those who were not, no significant difference in the level of any of the dependent variables Hct change, estimated blood loss and transfusion units was observed (p > .05).

Table 4: *Multiple Linear Regression Analysis for Predicting Change of Hct from SSRI*

	Unstandardized				
	β	SE	Beta	t	p
SSRI	.031	.77	.004	.04	.968
Pre-operative Hct	.282	.11	.286	2.64	.010
Age	.103	.05	.230	2.18	.032
BMI	-.131	.08	-.179	1.69	.096

Note. Overall model summary = F (4, 75) = 4.28, p = .004

To examine the change in hematocrit, a multiple regression analysis was conducted using SSRI, preoperative hematocrit, age, and body mass index. Table 3 shows the results from a multiple regression model predicting hematocrit change using SSRI, preoperative Hct, age and BMI as covariate. The overall model is statistically significant, F (4, 75) = 4.28, p = .004, but only predicted 18.6% of the total variance of Hct change which is not a strong model. Significant predictors in the model are pre-operative Hct (Beta = .286, p = .010) and age (*Beta* = .230, p = .032). Therefore, the only significant predictor of change Hct was:

- Age: Older individuals demonstrated higher levels of change in Hct. Age was thus significant when controlling for the effects of SSRI, pre-op Hb, pre-op Hct, and BMI.

The results thus indicate that there was no significant change in Hct in patients using serotonergic antidepressants in the pre-operative period prior to undergoing total knee arthroplasty. However, patients who used serotonergic antidepressants had a significantly lower pre-operative Hct compared to those who did not.

The second outcome measure was to determine if patients using serotonergic antidepressants and undergoing total knee arthroplasty were more likely to receive a greater amount of blood transfusions compared to those not using serotonergic antidepressants. To answer this question, estimates and standard deviations for the logistic regression model predicting the need for blood transfusion from SSRI, preoperative Hct and age was performed. Due to the particular distribution of the variable transfusion units (see Table 5), it is treated as a dichotomous variable in this model, where patients either required blood transfusion or they did not. The model is statistically significant, χ^2 (3) = 32.93, p < .001, Nagelkerke R^2 = .573. The only significant predictor in this model was preoperative Hct (B=–.666, p=.001, Odd's Ratio =.514), Where the odds of requiring blood transfusion were decreased as levels of preoperative Hct increased. Specifically, lower levels of pre-op Hct resulted in higher levels of blood transfusions. The conclusion from this analysis related to the research question is that patients on serotonergic antidepressants did not require greater amounts of blood transfusion.

Table 5: *Multiple Linear Regression Analysis for Predicting Transfusion Units from SSRI*

	β	*SE*	*Wald*	*OR*	*p*
SSRI	-.514	.87	.348	.60	.555
Pre-Op Hct	-.666	.20	11.320	.51	.001
Age	.082	.05	2.524	1.09	.112

Note: Overall model summary = χ^2 (3) = 32.93, p < .001, Nagelkerke R^2 = .573

The third outcome measure was to determine if patients using serotonergic antidepressants undergoing total knee arthroplasty experienced an increase in estimated blood loss compared to those not using serotonergic antidepressants. The mean estimated blood loss in the index group of antidepressant users was 63.1 ml (*SD* =51.01) and 46.75 ml (SD = 40.20) in the control group. Results from a multiple regression model predicting estimated blood loss from SSRI is shown in Table 6. This model was not statistically significant, F (1, 78) = 2.54, p = .115, R^2 = .032, indicating that SSRI usage was not a good predictor of estimated blood loss. The overall model was not significant and predicted as little as 3.2% of the variance in estimated blood loss. The conclusion from this analysis is that there was no significant difference in estimated blood loss between patients who used serotonergic antidepressants and those who did not, prior to undergoing total knee arthroplasty.

Table 6: *Multiple Linear Regression Analysis for Predicting Estimated Blood Loss from SSRI*

	Unstandardized				
	β	*SE*	*Beta*	*t*	*p*
SSRI	-16.375	10.27	-.178	-1.60	.115

Note: Overall model summary = F (1, 78) = 2.54, p = .115, R^2 = .032

4. Discussion

The association of bleeding complications with the use of serotonergic antidepressants has been a subject of debate ever since these drugs were introduced. Few studies have explored the effect of these drugs on perioperative bleeding, and evidence thus far is limited and inconclusive. Compared to previous studies, the current study of patients undergoing total knee arthroplasty who continued the use of serotonergic antidepressants in the preoperative period did not show an increase in perioperative bleeding. There was no significant difference in the three outcome measures of change in hematocrit, estimated blood loss, and perioperative transfusion requirements between patients who used serotonergic antidepressants and those who did not. In the study of Moving *et al.* [4]. The study population consisted of patients who underwent a variety of orthopedic surgeries. In the study by van Haelst et al. [14]. The study population consisted of patients who underwent total hip arthroplasty, and the outcome measures were estimated blood loss and blood transfusion requirement. It is interesting to note that the current study is the first study to focus exclusively on total knee arthroplasty using the tourniquet method, using the three outcome measures of change in hematocrit, blood transfusion requirement, and estimated blood loss.

The researcher deliberately chose to study the effects of only the specific serotonergic antidepressants, based on the binding properties of these drugs including only those considered as having high affinity for the serotonin reuptake transporter. Furthermore, this study investigated the effect of serotonergic antidepressants on perioperative bleeding in a highly standardized elective surgical procedure in a well defined population, such as total knee arthroplasty. In order to be objective, three outcome measures were utilized to determine a possible association with serotonergic antidepressant use and increased surgical bleeding. Sample selection was done in reverse chronological order from the computerized database to prevent selection bias. Change in hematocrit was calculated between the preoperative value and the lowest post operative hematocrit, in order to account for potential confounders of hemodilution and fluid shifts that occur during surgery. Blood transfusion is a highly accurate standardized procedure in this hospital, and is well documented in the blood bank record, and the transfusion note completed by the nurses. It is important to note that total knee arthroplasty patients in this hospital were transfused only if there was an acute drop in hematocrit, or if

the patients were symptomatic and exhibited signs of tachycardia, hypotension, lethargy or weakness.

There were several limitations to the current study. Firstly, this was a retrospective study of 80 patients, in a single center. Secondly, the documentation of estimated blood loss in the anesthesia record is not an accurate measurement as described in the literature. Thirdly, potential confounders such as tobacco use, chronic illnesses, alcohol abuse, co-medications, and duration of surgery were not utilized in this analysis. Fourthly, although patients were given written and verbal instructions regarding antiplatelet agents, NSAIDs, herbal supplements, and vitamins prior to the surgery, there were no measures to accurately assess if they actually adhered to the instructions. Finally, there is also the possibility that the sample size of 80 was insufficient to detect a significant difference in bleeding risk between users of serotonergic antidepressants and non-users.

5. Acknowledgments

- Dr. Enas Kandil, *MD*, University of Texas Southwestern, Dallas
- Terri Jones, *CRNA*, Department of Veterans Affairs, Dallas, Texas

6. References

1. McCloskey DJ, Postalache TT, Vittone BJ, Nghiem KL, Monsale JL, Wesley RA *et al.* Selective serotonin reuptake inhibitors: measurement of effect on platelet function. Transalational Research 2008; 151:168-172. doi: 10.1016/j.trsl2007.10.004
2. De Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: mechanisms, clinical outcomes and implications for use in elderly patients. Drugs & Aging 2011; 28(5):345-367. doi:10.2165/11589340-000000000-00000
3. Meijer WE, Heerdink ER, Nolen WA, Herings RM, Leufkens HG. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. Archives of Internal Medicine 2004; 164(21):2367-2370. Retrieved from http://archinte.jamanetwork.com/article.aspx?articleid=217660
4. Movig KL, Janssen MW, Malefijt JD, Kabel PJ, Leufkens HG, Egberts AC. Relationship of serotonergic antidepressants and need for blood transfusion in orthopedic surgical patients. Archives of Internal Medicine 2003; 163:2354-2358. doi:10.1001/archinte.163.19.2354
5. Dalton SO, Sorensen HT, Johansen C. SSRIs and upper gastrointestinal bleeding: What is known and how should it influence prescribing? [Review article]. CNS Drugs, 2006; 20(2):143-151.
6. Meijer WE, Heerdink ER, Nolen WA, Herings RM, Leufkens HG. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. Archives of Internal Medicine 2004; 164(21):2367-2370. Retrieved from http://archinte.jamanetwork.com/article.aspx?articleid=217660
7. De Abajo FJ, Garcia Rodriguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. British Medical Journal. 1999; 319:1106-1109.
8. De Abajo FJ, Montero D, Garcia Rodriguez LA, Madurga M. Antidepressants and risk of upper gastrointestinal bleeding. Pharmacology & Toxicology 2006; 98:304-310.
9. Napenas JJ, Hong CH, Kempter E, Brennan MT, Furney SL, Lockhart PB. Selective serotonin reuptake inhibitors and oral bleeding complications after invasive dental treatment. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 2011; 112:463-467. doi:10.1016/j.tripleo.2011.04.033
10. Cinar O, Cevik E, Kilic E, Kesim ME, Ak M. Ecchymosis due to sertraline use: a case report. Bulletin of Clinical Psychopharmacology 2010; 20(4):321-323. Retrieved from www.psikofarmakoloji.org
11. Van Cann EM, Koole R. Abnormal bleeding after an oral procedure leading to airway compromise in a patient taking selective serotonin reuptake inhibitor and a nonsteroidal antiinflammatory drug. Anesthesiology, 2008; 109(3):568-569. doi:10.1097/ALN.0b013e318182c88c
12. Looper KJ. Potential medical and surgical complications of serotonergic antidepressant medications. Psychosomatics 2007; 48:1-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17209143
13. Gartner R, Cronin-Fenton D, Hundborg HH, Pedersen L, Lash TL, Sorensen HT *et al.* Use of selective serotonin reuptake inhibitors and risk of re-operation due to post-surgical bleeding in breast cancer patients: a Danish population-based cohort study. BMC Surgery, 2010, 10(3). doi: 10.1186/1471-2482-10-3
14. Van Haelst IM, Egberts TC, Dooderman HJ, Traast HS, Burger BJ, Kalkman CJ, Van Klei WA. Use of sertonergic antidepressants and bleeding risk in orthopedic patients. Anesthesiology 2010; 112(3):631-636. doi: 10.1097/ALN.0b013e 3181cf8fdf
15. Sayadipour A, Mago R, Kepler CK, Chambliss RB, Certa KM, Vaccaro AR *et al.* Antidepressants and the risk of abnormal bleeding during spinal surgery: a case-control study. Eiropean Spinal Journal. 2012, 2132-2138. doi:10.1007/s00586-011-2132-8
16. Andreasen JJ, Riis A, Hjortdal VE, Jorgenson J, Sorensen HT, Johnsen SP. Effect of selective serotonin reuptake inhibitors on requirement for allogenic red blood cell transfusion following coronary artery bypass surgery. American Journal of Cardiovascular Drugs 2006; 6(4):243-250.
17. Huyse FJ, Touw DJ, Van Schijndel RS, De Lange JJ, Slaets JP. Psychotropic drugs and the perioperative period: A proposal for a guideline in elective surgery. Psychosomatics, 2006, 47:8-22. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16384803