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An evaluation of the effect of using selective seratonin re-uptake inhibitors on perioperative bleeding in gynecology patients

Jinekoloji hastalarında selektif seratonin geri alım inhibitörleri kullanmanın kanama üzerine etkisinin değerlendirilmesi

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ÖZ

Amaç: Çalışmanın amacı SSRİ kullanan ve değişik jinekolojik operasyonlar geçien hastalarda operasyon tipi, kanama miktarı, kan transfüzyon ihtiyacı ve transfüzyon yapılan kan miktarını değerlendirmektir.

Gereç ve yöntemler: Jinekolojik operasyon geçiren hastalarda retrospektif değerlendirme yapıldı. SSRİ kullanan ve kullanmayan hastalar peroperatif ve postoperatif hemoglobin, hematokrit, trombosit sayısı, aktive parsiyel tromboplastin zamanı (APTT), INR değeri; kan transfüzyonu ihtiyacı ve transfüze edilen kan miktarı açısından karşılaştırıldı.

Bulgular: Jinekolojik operasyon geçiren hastalarda SSRİ grubundan antidepresan ilaçların kanamada artmaya ve hemoglobin ve hematokrit değerlerinde düşmeye neden olmadığı görüldü. Gruplar arasında kan transfüzyonu ihtiyacı ve miktarı açısından istatistiksel olarak anlamlı fark bulunamadı.

Sonuç: Potansiyel kanama etkisi yüzünden SSRİ'lerinin preoperatif dönemde kullanımının kesilmesine gerek yoktur. Bu hastaları perioperatif dönemde yakın takip edilmesi ve kanama protokolünün dikkatli izlenmesi yeterlidir.

Anahtar kelimeler: kan transfüzyonu, jinekolojik operasyonlar, intraoperatif kanama, SSRİ

ABSTRACT

Aim: The aim of this study was to examine the effects of the use of SSRI by patients in different gynecological operations, through an evaluation of operation type, bleeding amount, requirement for blood and amount of blood transfused.

Materials and Methods: A retrospective evaluation was made of patients who underwent gynecological surgery. Patients who were taking and not taking SSRI were compared in respect of preoperative and postoperative hemoglobin, hematocrit, platelet count, activated partial thromboplastin time (APTT), INR values, requirement for blood transfusion, and amount of blood transfused.

Results: The use of antidepressant drugs by gynaecology patients was not seen to increase bleeding and caused no decrease in hemoglobin or hematocrit values. No statistically significant difference was determined between the groups in respect of the requirement and amount of blood transfusions.

Conclusion: There is no need to terminate the use of SSRI because of potential bleeding effects or to evaluate patients in respect of these effects. It can be considered sufficient to monitor these patients closely perioperatively and to carefully follow the bleeding protocol.

Keywords: blood transfusion, gynecological operations, intraoperative bleeding, SSRI

INTRODUCTION

Antidepressant drugs are one of the most frequently prescribed drugs worldwide. As 'selective serotonin re-uptake inhibitors' (SSRI) are safe, used more than other antidepressants, particularly in the elderly. Current evidence has drawn attention to a moderately increased risk of bleeding with increased patient sensitivity and risk factors with SSRI use (1). As SSRIs impair the serotonin (5HT) re-uptake mechanism of platelets, they reduce the amount of serotonin in platelets. This causes a sub-optimal start of the coagulation cascade and prolonged bleeding time (2) Although there are many studies related to increased bleeding with the use of SSRI, the majority have found that the effect is at a moderate level and the amount does not threaten patient safety. Seitz et al examined an elderly patient group who underwent surgery for hip fracture, and reported that although SSRIs caused an increase in erythrocyte transfusion, no increase was observed in complications, morbidity or mortality related to postoperative bleeding. . It was concluded that because discontinuation of the drug cannot be guaranteed in many patients as it can cause unwanted psychiatric complications, it is more appropriate for only the surgeon to be informed of this risk (3). The aim of this study was to investigate patients using and not using SSRI, in seven different gynecological operation groups, to determine whether or not there was any effect of the drug on bleeding in gynecological operations by comparing preoperative and postoperative blood values, the need for blood transfusion and the amounts.

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MATERIALS AND METHODS

The approval for this retrospective study was obtained from the Instutional Ethics Committee. From the hospital records, all the gynecological operations in 2015 were screened. Patients taking alaproclate, citalopram, escitalopram, etoperidon, fluoxetin, fluvoxamin, paroxetine, sertraline and zimelidine were included in the SSRI group (4).

Patients were excluded if they were aged <18 years, had any hemorrhagic disease, or were using anti-coagulants, warfarin, antiplatelet agents, NSAID, ASA, or any antidepressant other than SSRI. Patients using SSRI who had interrupted the usage within the previous 2 weeks or taken the drug irregularly were also excluded from the study. A total of 80 patients were identified who were using antidepressants and met the study inclusion criteria. The patients were grouped according to the operation types, which were the most frequently performed operations in our hospital. These groups were operative laparoscopy (ovarian cyst), conization, total abdominal hysterectomy and bilateral salpingo oopherectomy, probe curettage, grading surgery, vaginal hysterectomy and myomectomy. Patients applied with interventions other than these were not included in the study. Patients applied with more than one surgical procedure in the same session were not included as it was considered that the amount of bleeding could be different.

A control group was formed of a total of 365 patients who were not using antidepressants and met the above-mentioned criteria.

For each patient a record was made of the hemoglobin, hematocrit, platelet, INR, PT and APTT values preoperatively and at the second hour postoperatively. As postoperative INR, PT and APTT were not routinely examined, they were only recorded for patients where examined. It was recorded whether or not blood transfusion was applied during the operation, and if so, how many units of erythrocyte suspension were needed. These values were compared between the patients using SSRI and those not using SSRI in the seven different operation groups.

Statistical Analysis

All the statistical analyses were performed using SPSS 12.0.1 software (SPSS Inc, Chicago, IL, USA). To determine the effects of SSRIs and different operation types on blood loss, the data obtained were analysed using 2 x 7 Multivariate Variance Analysis. Thus, the roles were evaluated of operation type and SSRI use as independent variables, and together on two types of bleeding taken as a dependent variable. All the values were stated as mean ± standard deviation (SD).

To determine whether or not there was a greater likelihood of blood transfusion in patients using SSRIs than in those not using antidepressants, 2 x 2 Chi-square analysis was applied. In those applied with blood transfusion, the t-test was applied for comparisons of independent groups to determine whether SSRI use made any difference in the amount of blood transfused. Differences in the pre and postoperative blood values of the patients using and not using SSRIs were evaluated in dependent groups using the t-test and when parametric assumptions were not met (eg, <30 patients in the group <30), the Wilcoxon Signed Rank test.

RESULTS

To determine the effects of SSRIs and different operation types on changes in hemoglobin and hematocrit values, the data obtained were analysed using 2 x 7 Multivariate Variance Analysis. The scale points related to bleeding are shown as mean and SD values in Table 1.

Table 1. Mean and standard values related to the blood loss of patients

SSRI status	Operation	Hb loss		Hct loss		*n*
		mean	*SD*	*mean*	*SD*	
Using SSRI	opls	1.66	1.09	4.96	3.73	12
	conization	1.21	.59	3.61	1.57	10
	tah	1.28	1.34	3.99	4.05	29
	probe	.06	.46	.22	2.67	5
	grading	2.10	.87	7.76	3.55	5
	vah	2.54	1.09	7.52	2.99	11
	myomectomy	1.95	1.06	5.96	3.47	8
Not using SSRI	opls	1.35	.77	4.06	2.91	74
	conization	1.13	.73	3.44	2.68	49
	tah	1.54	1.27	5.07	3.24	139
	probe	.41	.59	1.41	1.51	15
	grading	2.93	1.67	8.40	5.63	15
	vah	2.62	1.14	7.82	3.49	43
	myomectomy	1.53	1.07	4.65	3.12	30

probe: probe curettage, vah: vaginal hysterectomy

The result of the Box M test showed that the variance homogeneity assumption was not met, so instead of Wilks λ, the Pillai criteria were used (Tabachnik and Fidell, 2007). The level of statistical significance was set at 0.05. To reduce Type I errors, Bonferroni correction was applied and the level of statistical significance was taken as 0.025 (0.05/2).

The analysis results showed that only the type of operation had a significant effect for hemoglobin and hematocrit; Pillai's trace =0.159, F (12, 862) =6.22, p<0.001, partial 2 =0.08. The basic effect of SSRI use and the joint effect of SSRI use and type of operation were not statistically significant (p>0.05). The use of SSRIs was not determined to have a statistically significant effect on bleeding.

The analysis made to determine whether or not there was a greater likelihood of blood transfusion in patients using SSRIs than in those not using SSRIs, showed no statistically significant difference between those using or not using SSRIs in respect of blood transfusion (p=0.11) (Table 2).

Table 2. Blood transfusion status according to SSRI status

SSRI use status	Blood transfusion				
	Applied		Not applied		
	No	%	No	%	Total
Using SSRI	7	8.8	73	91.3	80
Not using SSRI	16	4.4	349	95.6	365
Total	23	5.2	422	94.8	445

According to the analysis results to determine whether or not there was any difference in the amount of erythrocyte suspension between patients using or not using SSRIs, no statistically significant difference was determined in the amount of erythrocyte suspension applied in transfusion between the patients using SSRI (2.14±0.38 U) and patients not using SSRI (2.25±0.58) (p>0.05).

When the Plt, INR, PT and PTT values were compared separately in patients using and not using SSRIs, to determine whether there was any difference postoperatively, the t-test for dependent groups or the non-parametric Wilcoxon Signed Rank test was applied to the data obtained for each value. The mean and standard deviation values of Plt, INR, PT and PTT pre and postoperatively for the patients using and not using SSRIs are shown in Table 3.

Table 3. Mean and standard deviation values of Plt, INR, PT and PTT pre and postoperatively for the patients using and not using SSRIs.

	SSRI use					
	Using SSRI			Not using SSRI		
	Mean	*SD*	*n*	*Mean*	*SD*	*n*
Preoperative pplt	278037	58415	80	282561	78099	365
Postoperative pplt1	250200	59854	80	252879	70564	365
Preoperative INR	1.16	0.23	5	1.06	0.10	38
Postoperative INR1	1.26	0.21	5	1.19	0.11	38
Preoperative PT	12.44	2.39	5	11.39	1.10	38
Postoperative PT1	13.52	2.18	5	12.79	1.21	38
Preoperative PTT	30.54	3.62	5	31.77	2.47	38
Postoperative PTT1	29.22	1.51	5	28.35	4.86	38

The result of the t-test for dependent groups for the group using SSRIs showed a statistically significant decrease in the Plt values from preoperative (278037±58415) to postoperative (250200±59854) (p<0.001). The results of the Wilcoxon Signed Rank test determined a statistically significant increase in the postoperative INR and Pt values compared to the preoperative values (INR: 1.26±0.21 postoperative, 1.16 ± 0.23 preoperative; Pt: 13.52±2.18 postoperative, 12.44 ± 2.39 preoperative) (p<0.05). No statistically significant difference was determined between the preoperative and postoperative PTT values (p>0.05). In the results of the t-test for dependent groups, statistically significant differences were determined between the preoperative and postoperative Plt, INR, Pt, and PTT values (p<0.001 for all). The preoperative mean Plt and PTT values were significantly higher than the postoperative values (Plt: 282561± 7809, Ptt: 31.77 ±2.47 preoperative; Plt: 252879 ± 70564, Ptt: 28.35 ± 4.86 postoperative). The mean INR and Pt values were significantly higher postoperatively compared to the preoperative values (INR: 1.19 ± 0.11, Pt: 12.79 ± 1.21 postoperatively; INR: 1.06 ± 0 .10, Pt: 11.39 ± 1.10 preoperatively). (Table 4).

Table 4. The relationships of the comparison of pre and postoperative Plt, INR, Pt and aPtt values in patients using and not using SSRIs.

	Using SSRI				Not using SSRI			
	mean	*SD*	*n*	*p*	*mean*	*SD*	*n*	*p*
Preoperative pplt	278037.49	58415.25	80	**.000**	282561.64	78099.99	365	**.000**
Postoperative pplt1	250200	59854.34	80		252879.45	70564.88	365	
Preoperative INR	1.16	0.23	5	**.043**	1.06	0.10	38	**.000**
Postoperative INR	1.26	0.21	5		1.19	0.11	38	
Preoperative PT	12.44	2.39	5	**.043**	11.39	1.10	38	**.000**
Postoperative PT	13.52	2.18	5		12.79	1.21	38	
Preoperative aPTT	30.54	3.62	5	.345	31.77	2.47	38	**.000**
Postoperative aPTT	29.22	1.51	5		28.35	4.86	38	

The mean and standard deviation values related to the change in Plt, INR, PT and PTT values from preoperative to postoperative are shown in Table 5. No statistically signifcant difference was observed in the preoperative to postoperative change in Plt, INR, PT and PTT values (p>0.05) (Table 5).

Table 5. The change in pre and postoperative Plt, INR, Pt and aPtt values in patients using and not using SSRIs.

	Using SSRI			Not using SSRI			*p*
	mean	*SD*	*n*	*mean*	*SD*	*n*	
Change in Platelet value	27837	34687	80	29682	50509	365	0.642
Change in PT value (secs)	1.08	0.64	5	1.39	0.68	38	0.338
Change in APTT value (secs)	1.32	2.95	5	3.42	4.24	38	0.128
Change in INR value	0.10	0.06	5	0.12	0.06	38	0.345

DISCUSSION

The results of this study showed that the use of antidepressant drugs by gynecological patients did not cause a decrease in the hemoglobin or hematocrit values. Just as there was no statistically significant effect of SSRI use on bleeding (decrease in hemoglobin and hematocrit values), when the groups were evaluated together there was not seen to be any reduction effect. No significant difference was observed between the patients taking or not taking SSRIs in respect of the need for blood transfusion, nor was there any statistically signficant difference between the groups in respect of the amount of blood transfusion.

The risk has been found to be similar in different types of SSRI in relation to the effect mechanism (5). Therefore, all the SSRIs in the current study were evaluated under a single heading rather than separately.

Of the total serotonin in the blood, 99% is stored in the platelets, and when there is a thrombotic event, it is released causing vasoconstriction and platelet aggregation. Platelets can not synthesize serotonin and there is a need for re-uptake of serotonin from the plasma. Therefore, through inhibition of re-uptake in the platelet cell membrane, SSRIs reduce intracellular serotonin, thereby causing reduced aggregation (6). SSRIs inhibit the protein (5HTT) that provides the re-uptake of serotonin from the plasma membrane, which is a glycoprotein embedded in the plasma membrane. The increased risk of bleeding has been associated with low platelet serotonin content and a reduction in platelet aggregation induced by ADP, collagen and adrenalin (7). Other effects increasing the tendency to bleeding are a reduction in platelet binding affinity, reduced calcium mobilisation and reduced platelet secretion, which is a collagen response (8).

The surgical procedure itself has been associated with a reduced platelet serotonin level and simultaneously elevated plasma serotonin level (9). The combined effect of surgery and drugs can result in impaired hemostasis and consequently a high risk of bleeding in patients using SSRIs (10).

It has been reported that at least 60 days of use are required for antidepressant drugs to show an antiplatelet effect (11). In clinical studies, a reduction of 80%-90% in platelet serotonin stores has been observed following a few weeks of treatment (12).

SSRIs affect platelet aggregation and this can be evaluated with platelet function tests. The PT, PTT and INR, which evaluate the enzymatic cascade forming the fibrin clot, are not changed by SSRIs. Mago et al recommended the consideration of the platelet function test before elective surgery in patients taking SSRIs, but no clear data about the usefulness of this test could be shown (13).

Several studies have shown that SSRIs could lead to bleeding problems in orthopaedic interventions (10). Moving et al reported that while patients using SSRIs required perioperative blood transfusion in orthopaedic surgery, non-serotonergic drugs did not show this effect. The risk of blood transfusion was found to be 4-fold higher in patients using SSRIs and as SSRI use is widespread in the elderly, a significant number of patients are exposed to this risk (14).

The risk of gastrointestinal bleeding has been determined to be 3.6-fold higher in those using drugs compared to those not taking any medication (13). The use of SSRIs during pregnancy has been reported to double the risk of postpartum bleeding

and anaemia (4). The likelihood of hospitalisation because of upper gastrointestinal tract bleeding has been found to be 3.6-fold greater in those using SSRIs compared to population not taking any drugs (5).

Although there are many studies reporting that SSRI use increases bleeding, there are also studies that have reached a completely opposite conclusion or that the increased bleeding is not of a level to affect the patient status. Due to the retrospective design of studies, it may not be possible to measure blood losses or evaluate a re-operation decision objectively. In addition, depression itself may cause poor surgical results (15).

Harirchian et al found no causal relationship between SSRI use and postoperative bleeding and reported that even if there was a small increase in the risk of postoperative bleeding with SSRI use, the number of hematoma in patients using and not using SSRI were comparable. Thus, it was reported that the use of SSRI had no negative effect on bleeding in the perioperative period, and it was concluded that the use of SSRIs was safe and there was no need for the use to be terminated in cosmetic facial surgery patients (16).

In a study conducted to determine whether or not SSRI use caused any increase in perioperative bleeding in spinal surgery, the increase in blood loss was not significant and the benefit of the drug outweighed the harm. However, in more complicated spinal surgery patients, taking the risk of severe bleeding into account, it can be considered more appropriate to change the medication or to apply a platelet function test (17).

The need for re-operation because of bleeding following breast surgery has been reported to rise from 3% to 7% in patients using SSRIs but it has been suggested that the depression treatment of the patient should not be discontinued without evaluating the risks and benefits of this difference (18).

In patients using SSRIs undergoing primary total hip arthroplasty, an increase of 100 ml has been observed in blood loss during surgery. This loss has not increased the amount of perioperative blood transfusion. When the risks of increased bleeding are compared with the risks of halting antidepressant use, it has been reported that it is more rational to terminate the drugs but the patient must be well evaluated and followed up closely (10).

Untreated depression can cause problems such as immune dysfunctions, immobility, and cigarette smoking (19). Moreover, many patients experience physical, psychological and somatic problems after terminating antidepressants (20).

Discontinuing treatment when the patient has a need for greater motivation and energy for getting dressed, wound care and preoperative and postoperative follow-up can cause the return of depression and anxiety in the perioperative process (16). In addition, discontinuing antidepressants without a tapering reduction can cause anxiety, agitation, insomnia and nausea, thereby making postperative care more difficult (20).

Finally, not continuing with sufficient required treatment postoperatively can cause increased mortality rates in patients with depression (21). Valuck et al reported a 61% increase in the risk of suicide in the first 2 weeks after terminating antidepressants (22).

The decision for preoperative antidepressant use should be evaluated according to the patient in respect of the severity of the depression and the type of antidepressants used. In cases of moderate and severe depression, it may be appropriate to change the antidepressants to non-serotonergic drugs such as bupropion or mirtazapine (15). Terminating antidepressants before surgery without sufficent examination and evaluation must be avoided (23).

Experimental animal studies have shown that for a return to normal serum levels of 5HT (5-hydroxytryptamine) and the 'main metabolite' 5HIAA (5-hydroxyindoleacetic acid), there should be a termination period of SSRIs of at least 1-2 weeks (24). When it is decided to terminate drugs, a 2-week period has been shown to be sufficient for platelet life and 5HT and 5HIAA serum levels to return to normal (24,25).

In the light of all these results, although the use of SSRIs has been observed to increase the amount of bleeding in some circumstances, no severe effect on bleeding is seen, as demonstrated by the current study results. Preoperatively, preparations must be made taking the increased possibility of a need for blood transfusion, and it is thought that for patients using SSRIs, increasing the amount of blood routinely prepared for severe surgical cases, and awareness of the surgical team of the effect of the drug are sufficient precautions. Terminating treatment of patients because of the effect of the drug on bleeding, which would leave them defenceless in the difficult and traumatic perioperative period, is not appropriate. However, in difficult cases, rather than terminating the drugs it is appropriate to continue treatment with an antidepressant other than SSRI.

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