ORIGINAL ARTICLE

Comparison of pre-operative platelet functions by thromboelastogram in patients selective serotonin reuptake inhibitors user and non-user

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ABSTRACT

BACKGROUND: The use of antidepressant drugs, in particular selective serotonin reuptake inhibitors (SSRIs), has increased in recent years. Using SSRIs can cause changes in serotonin metabolism. Serotonin provides platelet aggregation and plays a role in the regulation of vascular tone and coagulation processes. The aim of this study was to evaluate the effects of SSRI use on coagulation functions with thromboelastogram (TEG) in patients undergoing surgical operation and to compare with non-user cases.

METHODS: The study was designed for 60 patients whose physical status was classified according to the American Society of Anesthesiology (ASA) classification as ASA I–II were included in the study. During routine pre-operative blood tests, 2 ml complete blood sample used and TEG performed. The cases were divided into two groups as SSRI user and non-user and analyzed.

RESULTS: R value was higher in SSRI user patients than in non-user patients. The MA value was significantly lower in SSRI user. There was no statistically significant difference in other parameters. In the evaluation based on duration of SSRI use, there was no statistically significant difference between those whose duration of use was more than 1 year and <1 year.

CONCLUSION: When the coagulation process was evaluated by TEG method, it was seen that the onset of clotting was prolonged and thrombus formation was slowed down in SSRI users. The results did not reveal that SSRI alone was the cause of bleeding, but it was concluded that slowing the process might be important, especially for surgical operations.

Keywords: Platelet functions; selective serotonin reuptake inhibitors; thromboelastogram.

INTRODUCTION

The use of antidepressant drugs, in particular selective serotonin reuptake inhibitors (SSRIs), has increased in recent years.[1] This increase in SSRI use can be attributed to a lower side effect profile compared to conventional antidepressants. However, the use of SSRIs is not completely risk free and can cause serious hematological side effects.[2–4]

Serotonin provides platelet aggregation and plays a role in the regulation of vascular tone and coagulation processes. SSRIs inhibit serotonin reuptake by inhibiting the active membrane transport mechanism and consequently increasing the amount of serotonin in the synaptic cleft. SSRIs may increase the amount of serotonin in the central nervous system and cause a decrease in the amount of serotonin in the platelets. Therefore, this may lead to a decrease in platelet aggregation and an increased risk of bleeding.[4–6]

The aim of this study was to evaluate the effects of SSRI use on coagulation functions with thromboelastogram (TEG) in patients undergoing surgical operation for inguinal hernia and to compare with non-user cases.

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MATERIALS AND METHODS

Patients

The study was conducted with the approval of the ethics committee (October 02, 2017-2017/149) and carried out in the operating room of our hospital between January and July 2018 in accordance with the Helsinki Declaration. The study was designed for patients with a history of SSRI drug use in whom elective inguinal hernia surgery was planned and 60 patients whose physical status was classified according to the American Society of Anesthesiology (ASA) classification as ASA I were included in the study.

Cases with a history of any drug use, cases with chronic alcohol, tobacco, or substance abuse, patients with a known disease that may cause a bleeding disorder, and those who refused to volunteer were excluded from the study. Cases using SSRI were Group S (n=30) and those not using SSRI were Group C (n=30).

Study Design

Demographic data, medications, and duration of use of the patients who were admitted to the anesthesia outpatient clinic for preoperative evaluation and included in the study were recorded. During routine pre-operative blood tests, 2 ml complete blood sample was separated into a citrated tube for TEG. In operating room, as the standard monitorization; electrocardiography, non-invasive blood pressure, pulse oximetry, NMT, end-tidal carbon dioxide, and temperature were followed up. For the induction, both of groups maintained with 1–2 mg/kg propofol and 1 µg/kg remifentanil injection. For the maintenance of anesthesia, both groups were administered intravenous (iv) 0.25 µg/kg/min remifentanil infusion and 1 MAC sevoflurane as the inhaler agent. Surgical duration and intraoperative bleeding amounts were recorded.

Thromboelastometry Analysis

Thrombelastography analysis was performed on a TEG_5000, version 4.2 (Haemoscope Corporation, Niles, IL, USA). One milliliter whole blood was taken from the citrated tube and transferred to the kaolin tube. The whole blood was gently mixed for full contact with the kaolin. A 340 µl of the mixture was taken with an automatic pipette and placed in the test bath. To antagonize the citrate, 20 µl of calcium chloride was added to the test bath with an automatic pipette. The test was initiated.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS), Inc., Chicago, IL, SPSS 18.00 was used for the analysis of the collected data. The obtained continuous variables were expressed as mean±SD or number (%). Number and % values were used in the presentation of categorical variables. The suitability of the obtained data to the normal distribution was carried out using the Kolmogorov–Smirnov test. The Mann–Whitney U-test was used for the analysis of continuous variables (age, weight, etc.). Chi-square test was used to compare two groups and to examine categorical variables. P<0.05 was considered statistically significant.

RESULTS

Sixty patients were included in the study. The mean age of the patients included in the study was 40.43±12.42 years in Group S and 40.97±9.75 years in Group C. In Group S, 60% (n=18) were female and 40% (n=12) were male, whereas in

Table 1. Distribution of the cases based on ASA score

Group S (n=30)		Group C (n=30)	
ASA I	ASA II	ASA I	ASA II
19 (63.3%)	11 (36.7%)	22 (73.3%)	8 (26.6%)

ASA: American Society of Anesthesiology.

Table 2. Distribution of cases according to reason for SSRI use in Group S

Reasons for SSRI use in Group S (n=30)			
Panic Dis.	OCD	Anxiety	Depression
6 (20%)	6 (20%)	11 (36.7%)	7 (23.3%)

OCD: Obsessive compulsive disorder; SSRI: Selective serotonin re-uptake inhibitor.

Table 3. Distribution of cases according to SSRI agents used in Group S

Distribution of SSRI agents in Group S (n=30)			
Fluoxetine	Sertraline	Paroxetine	Escitalopram
6 (20%)	8 (26.7%)	9 (30%)	7 (23.3%)

SSRI: Selective serotonin re-uptake inhibitor.

Table 4. Coagulation parameters and intraoperative bleeding

	Group S	Group K	p-value
PT (sec)	10.38±1.86	10.51±1.50	0.773
aPTT (sec)	35.07±6.17	35.03±4.65	0.976
PLT	188.30±43.92	187.37±42.20	0.933
Bleeding time (sec)	119.00±43.58	114.67±44.93	0.706

PT: Prothrombin time; aPTT: Activated partial thromboplastin time; PLT: Platelet.

Table 5. Comparison of the TEG parameters of the groups

Parameters of the groups	Group S	Group C	p-value
R (min)	5.56±1.23	4.37±1.07	**<0.001***
K (min)	2.09±0.61	2.04±0.54	0.723
α angle (deg)	60.74±6.70	63.79±6.54	0.079
MA (mm)	59.39±4.62	62.20±5.39	**0.034***
L30 (%)	2.26±1.84	2.62±1.95	0.466
CI	0.10±1.71	0.58±1.54	0.111
G (d/sc)	8.62±1.86	7.32±1.37	**0.003***

*P<0.05 is statistically significant. TEG: Thromboelastogram; R: Reaction time; K: Kinetics; α: Alpha angle (slope between R and K points); MA: Maximum Amplitude); L30: 30th minute lysis; CI: Clotting index; G: Clot elasticity at the specific time of reaching the MA.

Table 6. Comparison of TEG parameters based on duration of SSRI use

Duration of SSRI use	<1 year (n=18)	≥1 year (n=12)	p-value
R (min)	5.52±1.28	5.60±1.20	0.855
K (min)	1.97±0.52	2.29±0.71	0.159
α angle (deg)	62.50±4.95	58.10±8.24	0.078
MA (mm)	63.56±5.26	60.18±5.12	0.092
L30 (%)	2.24±1.87	2.28±1.88	0.965
CI	0.29±1.43	-0.70±1.96	0.120
G (d/sc)	8.98±1.97	8.07±1.60	0.191

TEG: Thromboelastogram; SSRI: Selective serotonin reuptake inhibitor; R: Reaction time; K: Kinetics; α: Alpha angle (slope between R and K points); MA: Maximum Amplitude); L30: 30th minute lysis; CI: Clotting index; G: Clot elasticity at the specific time of reaching the MA.

Group C, 50% (n=15) were female and 50% (n=15) were male. There was no statistical difference between the two groups (age [p=0.060] and sex [p=0.302]). The demographic distribution of the groups is shown in Tables 1–3. Coagulation parameters and intraoperative bleeding are shown in Table 4. The comparison of the TEG parameters of the groups is shown in Table 5. When the duration of SSRI use in Group S was evaluated over 1 year, 60% (n=18) had shorter than 1 year, and 40% (n=12) had a drug use duration of 1 year or more. The comparison of TEG parameters according to duration of use is shown in Table 6.

DISCUSSION

In this study, R value was higher in SSRI-treated patients than in non-SSRI-treated patients. The MA value was significantly lower in Group S. There was no statistically significant difference in other parameters. In the evaluation based on duration of SSRI use, there was no statistically significant difference between those whose duration of use was more than 1 year and <1 year.

Although surgical intervention itself is an important factor that disrupts the physiology of hemostasis, drugs used in the perioperative period have various effects on hemostasis and platelet functions. This situation affects the chance of surgical success, especially in large surgical interventions, and necessitates the follow-up of the hemostasis in the perioperative period.[7–9]

Five children aged between 8 and 15 years have been reported to have bruises or nosebleeds 1 week–3 months after starting SSRI treatment. In these cases, symptoms could be explained by the effects of SSRI on platelets.[10] It has been reported that the use of SSRIs increases the incidence of epistaxis and ecchymosis, possibly due to deterioration of platelet function. Although hemorrhage is rare, hematologic complications may occur in patients with major depression following treatment with SSRIs.[11]

In this study, coagulation process was evaluated with TEG in patients using SSRIs. The main purpose of this study was to investigate the effects of SSRIs on the coagulation process and to predict surgical bleeding in the pre-operative period. When the literature is examined, it is seen that the effects of SSRIs on coagulation have been examined by various laboratory techniques; however, a study evaluating this process with TEG in these cases was not encountered.

During primary hemostasis, various interactions occur between the platelets and the damaged vessel wall. Initially, platelets collected as a result of loss of the endothelial layer in the damaged area of the vessel wall undergo "platelet activation." Adhesion of the platelets to the subendothelial matrix occurs as a result of the interaction of the glycoprotein complex on the platelet surface and the plasma von Willebrand factor. ADP and serotonin are released from dense granules of activated platelets. Serotonin activates 5-HT2A receptors on the platelet membrane, and thus, platelet aggregation begins. Platelets collected in the region interact with each other. In this process, fibrinogen binds to specific platelet receptors.[4,12,13]

Serotonin can be freely found in plasma and stored in platelets. Because of the effects of serotonin on the pathophysiology of depression, most antidepressants have a direct effect on serotonin levels.[14] Hervig and Farstad reported a significant relationship between endogenous serotonin content in platelets, percentage of serotonin released, and platelet quality.[15]

Antidepressants that inhibit the reuptake of serotonin into platelets cause a decrease in and depletion of platelet serotonin reserves. This may inhibit serotonin-induced platelet aggregation amplification.[16] In the study, no distinction was made between the agents considering the similar mechanism of the action of all SSRIs.

Various laboratory techniques are used to evaluate the coagulation process. Thromboelastography is easy to perform and takes approximately 30 min. It allows coagulation to be evaluated in many ways and aids targeted treatment planning.[17] In the study, blood samples were taken from the patients in the pre-operative preparation stage, and two groups, SSRI and non-SSRI, were formed. TEG parameters were analyzed between the groups, and within Group S based on duration of SSRI use, taking 1 year as the classification point.

Geiser et al.[18] evaluated the hemostasis process according to the anxiety and SSRI usage of the patients based on activated partial thromboplastin time (aPTT), prothrombin time, INR and factor levels. The study reported high levels of plasmin-a2-antiplasmin complex, an indicator of fibrinolytic activity, and long aPTT in patients who were using SSRIs independent of anxiety. In the literature review compiled by Roose and Rutherford, the risk of perioperative bleeding was increased in patients using SSRI. However, the available data were insufficient to identify patients who could have increased bleeding.[19] In the study, it was seen that R time was significantly prolonged in Group S when compared to the control group. The decrease in the MA value, which is an indicator of platelet functions, proves that the use of SSRI negatively affects platelets during the hemostasis process. Considering the duration of use in the study, it was seen that R time and k time were prolonged, α angle decreased, and MA decreased in SSRI use for 1 year or more. Although as the duration of drug use increased, the influence on the platelets (hypocoagulability) was increased, the results were not statistically significant and this hypothesis could not be based on evidence.

It has been proven that with surgical stress, predisposition to hypercoagulability and decreased fibrinolysis occurs.[20] To avoid the effects of this situation, the study was designed for the patients in the pre-operative period. Considering surgical hypercoagulability, the use of SSRI may reduce the risk of venous thromboembolism.

In the pre-operative period, none of the patients had any bleeding problems. Although there were significant differences between the groups in the TEG values at the beginning of the coagulation process, the mean values of the TEG parameters of the groups were measured in the reference ranges and as normal. Results were clinically consistent with the absence of bleeding problems.

The fact that the surgical operations were not standardized and that the bleeding during the operation was not compared with the TEG findings limits the study. It is an issue to investigate whether significant differences between the groups show changes in bleeding findings during surgery. Furthermore, detailed studies on the effects of SSRI use on coagulation and the effect of SSRI use on surgical hypercoagulability can be planned.

Conclusion

When the coagulation process was evaluated using TEG method, it was seen that the onset of clotting was prolonged and thrombus formation was slowed down in SSRI users. The results did not reveal that SSRI alone was the cause of bleeding, but it was concluded that slowing the process might be important, especially for surgical operations. These data obtained from TEG may show significant results in operations with a high risk of bleeding. Additional studies are needed to demonstrate the effects on surgical bleeding.

Ethics Committee Approval: This study was approved by the Necmettin Erbakan University Meram Faculty of Medicine Ethics Committee (Date: 02.10.2017, Decision No: 2017-2017/149).

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Conflict of Interest: None declared.

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REFERENCES

1. Bismuth-Evenzal Y, Gonopolsky Y, Gurwitz D, Iancu I, Weizman A, Rehavi M. Decreased serotonin content and reduced agonist-induced aggregation in platelets of patients chronically medicated with SSRI drugs. J Affect Disord 2012;136:99–103. [CrossRef]
2. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: Population based cohort study. BMJ 2011;343:d4551. [CrossRef]
3. Verdel BM, Souverein PC, Meenks SD, Heerdink ER, Leufkens HG Egberts TC. Use of serotonergic drugs and the risk of bleeding. Clin Pharmacol Ther 2011;89:89–96. [CrossRef]
4. Skop BP, Brown TM. Potential vascular and bleeding complications of treatment with selective serotonin reuptake inhibitors. Psychosomatics 1996;37:12–6. [CrossRef]
5. Oyesanmi O, Kunkel EJ, Monti DA, Field HL. Hematologic side effects of psychotropics. Psychosomatics 1999;40:414–21. [CrossRef]
6. Halperin D, Reber G. Influence of antidepressants on hemostasis. Dialogues Clin Neurosci 2007;9:47–59. [CrossRef]
7. Aylı M, Şekerci S. Hemostasis problems, transfusion and blood conservation techniques in cardiovascular surgery. Turk Klin J Anest Reanim 2008;6:145–8.
8. Demir M, Tekgündüz E. Perioperative hemostatic evaluation: Scientific letter. Turk Klin J Med Sci 2008;28:361–8.
9. Kozek-Langenecker SA. The effects of drugs used in anaesthesia on platelet membrane receptors and on platelet function. Curr Drug Targets 2002;3:247–58. [CrossRef]
10. Lake MB, Birmaher B, Wassick S, Mathos K, Yelovich AK. Bleeding and selective serotonin reuptake inhibitors in childhood and adolescence. J Child Adolesc Psychopharmacol 2000;10:35–8. [CrossRef]

11. Mirsal H, Kalyoncu A, Pektaş O. Ecchymosis associated with the use of fluoxetine: Case report. Turk Psikiyatr Derg 2002;13:320–4.
12. Lippi G, Favaloro EJ, Salvagno GL, Franchini M. Laboratory assessment of perioperative management of patients on anitplatelet therapy: From bench to the bedside. Clin Chim Acta 2009;405:8–16. [CrossRef]
13. Miller JL, Rao AK. Blood platelets and von Willebrand disease. In: McPherason RA, Pincus MR, editors. Henry's Clinical Diagnosis and Management by Laboratory Methods. 22nd ed. Philadelphia, PA: Elseiver-Saunders; 2011. p. 801–22. [CrossRef]
14. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: Focus on the serotonin transporter. Clin Chem 1994;40:288–95. [CrossRef]
15. Hervig TA, Farstad M. Human blood platelet serotonin studied in vitro: Endogenous serotonin may stimulate thrombin-induced serotonin release in stored platelets. Platelets 1996;7:53–7. [CrossRef]
16. Pai VB, Kelly MW. Bruising associated with the use of fluoxetine. Ann Pharmacother 1996;30:786–8. [CrossRef]
17. Whitten CW, Greilich PE. Thromboelastography: Past, present, and future. Anesthesiology 2000;92:1223–5. [CrossRef]
18. Geiser F, Conrad R, Imbierowicz K, Meier C, Liedtke R, Klingmüller D, et al. Coagulation activation and fibrinolysis impairment arereduced in patients with anxiety and depression when medicated with serotonergic antidepressants. Psychiatry Clin Neurosci 2011;65:518–25. [CrossRef]
19. Roose SP, Rutherford BR. Selective serotonin reuptake ınhibitors and operative bleeding risk: A review of the literature. J Clin Psychopharmacol 2016;36:704–9. [CrossRef]
20. Gibbs NM. The effect of anaesthetic agents on platelet function. Anaesth Intensive Care 1991;19:495–505. [CrossRef]

ORİJİNAL ÇALIŞMA - *ÖZ*

Seçici serotonin geri alım inhibitörü kullanan ve kullanmayan hastalarda ameliyat öncesi trombosit fonksiyonlarının tromboelastogram ile karşılaştırılması

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AMAÇ: Antidepresan ilaçların, özellikle seçici serotonin geri alım inhibitörlerinin (SSRI'lar) kullanımı son yıllarda artmıştır. SSRI'ları kullanmak serotonin metabolizmasında değişikliklere neden olabilir. Serotonin, trombosit agregasyonu sağlar, vasküler tonusun düzenlenmesinde ve pıhtılaşma süreçlerinde rol oynar. Bu çalışmanın amacı cerrahi operasyon planlanan olgularda SSRI kullanımının pıhtılaşma fonksiyonları üzerine etkilerini tromboelastogram (TEG) ile değerlendirmek ve kullanmayan olgularla karşılaştırmaktır.

GEREÇ VE YÖNTEM: Çalışma, fiziksel durumu Amerikan Anesteziyoloji Derneği (ASA) sınıflandırmasına göre ASA I-II olarak sınıflandırılan 60 hasta için tasarlandı. Ameliyat öncesi hazırlık aşamasında rutin kan tetkiklerine ek olarak 2 ml tam kan örneği kullanıldı ve TEG analizi yapıldı. Hastalar SSRI kullanıcısı ve kullanmayan olmak üzere iki gruba ayrılarak incelendi.

BULGULAR: R değeri SSRI kullanan grupta anlamlı olarak yüksek izlendi. SSRI kullanan grubun MA değeri anlamlı olarak düşüktü. Diğer parametrelerde istatistiksel olarak anlamlı bir fark yoktu. SSRI kullanım süresine göre yapılan değerlendirmede, kullanım süresi bir yıldan uzun ve bir yıldan az olanlar arasında istatistiksel olarak anlamlı bir fark yoktu.

TARTIŞMA: Tromboelastogram yöntemi ile pıhtılaşma süreci değerlendirildiğinde, SSRI kullananlarda pıhtılaşma başlangıcının uzadığı ve trombüs oluşumunun yavaşladığı görüldü. Sonuçlar kanamanın tek başına SSRI olduğunu ortaya koymadı, ancak sürecin yavaşlatılmasının özellikle cerrahi operasyonlar için önemli olabileceği sonucuna varıldı.

Anahtar sözcükler: Tromboelastogram; trombosit fonsiyonları; seçici serotonin geri alım inhibitörleri.

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