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Research Article / Araştırma

Effects of Acetyl Salicylic Acid on the Risk of Thrombosis in Patients Undergoing Thoracic Surgery

Göğüs Cerrahisi Ameliyatı Geçiren Hastalarda Asetil Salisilik Asidin Tromboz Riski Üzerine Etkisi

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ABSTRACT

Objectives: Drug withdrawal in the pre-operative period may cause risks such as rebound phenomenon or thrombosis. We aimed to determine the incidence of thrombotic complications that may be associated with the discontinuation of pre-operative aspirin in thoracic surgery.

Methods: A comparison of demographics, pre-operative and post-operative hemoglobin levels, the duration of surgery, the length of intensive care unit (ICU) and hospital stay, perioperative transfusion of blood products, and the amount of perioperative bleeding was conducted between the patients who were administered Aspirin during their treatment and whose use of medication was discontinued 5 days before the surgery in the preoperative period and the patients who underwent surgery while aspirin treatment was going on.

Results: Of the observed complications, 11 were pulmonary embolism while three were re-exploration, one was gastrointestinal bleeding, and one was upper extremity deep vein thrombosis. The demographics, the duration of surgery, the length of hospital stay, and the use of perioperative blood products did not differ between the groups. The amount of perioperative bleeding and the length of ICU stay were significantly greater in group continued ($p<0.005$).

Conclusion: The discontinuation of aspirin may have a negative effect on patient outcomes in thoracic surgery.

Keywords: Antithrombotic agents, bleeding, complication, pulmonary embolism, thoracic surgery

ÖZ

Amaç: Preoperatif dönemde ilaç kesilmesi rebound fenomeni veya tromboz gibi durumlara yol açabilmektedir. Bu çalışmada, göğüs cerrahisinde preoperatif asetil salisilik asidin kesilmesi sonucunda oluşabilecek trombotik komplikasyon insidansının belirlenmesi amaçlanmıştır.

Yöntem: Preoperatif dönemde, operasyondan beş gün önce asetil salisilik asit tedavisi kesilen hastalar ile tedavisi devam ederken opere edilen hastaların demografik verileri, preoperatif ve postoperatif hemoglobin düzeyleri, ameliyat süresi, yoğun bakım ünitesi ve hastanede kalış süresi, perioperatif kan ürünü transfüzyonu ve perioperatif kanama miktarı karşılaştırıldı.

Bulgular: Gözlenen komplikasyonların 11'i pulmoner emboli, üçü yeniden eksplorasyon, biri gastrointestinal kanama ve biri üst ekstremite derin ven trombozu idi. Demografik özellikler, ameliyat süresi, hastanede kalış süresi ve perioperatif kan ürünleri kullanımı açısından gruplar arasında farklılık gözlemlenmedi. Perioperatif kanama miktarı ve yoğun bakımda kalış süresi kesilen grupta anlamlı olarak daha fazlaydı ($p<0,005$).

Sonuç: Göğüs cerrahisinde asetil salisilik asidin kesilmesi hasta sonuçlarını olumsuz etkileyebilmektedir.

Anahtar sözcükler: Antitrombotik ilaçlar, göğüs cerrahisi, kanama, komplikasyon, pulmoner emboli

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Introduction

Management of perioperative anticoagulation requires an interdisciplinary approach to provide temporary cessation of anticoagulation. Considering the bleeding and thrombotic risks, anticoagulant treatment may be temporarily suspended and parenteral anticoagulation can be initiated with the drugs acting on different pathways.[1] It is predicted that the thrombotic complications will increase significantly even more in the coming years.[2] It was revealed that the incidence of thrombotic complications increases further when antithrombotic therapy is discontinued preoperatively.[3] Especially in non-cardiac surgeries, increased risk of stent thrombosis, myocardial infarction, and death may be occurred in patients undergoing surgery immediately after stent implantation and in the presence of discontinuation of antiplatelet medication. In addition, the risks associated with the discontinuation of aspirin and the potential benefits of continued medication have been well reported in patients with cardiac stents.[4-6] In growing body of researches, it was revealed that the continuation of aspirin in patients taking aspirin for secondary cardiovascular protection during perioperative period, does not increase complications due to bleeding and decreases thrombotic complications. When aspirin is discontinued before surgery, aspirin withdrawal syndrome may develop.[6] However, patients receiving antiplatelet agents are still supposed to stop taking all these drugs at least 5 days before thoracic surgery in many institution, despite of well-known complications related with discontinuation of aspirin and current guidelines' recommendations.[7]

Therefore, on the basis of current situation, clinicans still have dilemma whether contunation of aspirin therapy in the pre-operative period. Primary outcome of this study is to investigate the incidence of thrombotic complications within the post-operative 48 h in patients whose aspirin therapy was discontinued. The secondary outcome is to determine hemorrhagic complications due to aspirin treatment.

Methods

After receiving the approval of the Local Ethics Committee (protocol number: 09.2018.140) and informed consent from the patients, this study was designed as a prospective, observational cohort study. The data of patients who underwent major thoracic surgery in our university hospital between January 2018 and January 2019 were evaluated. The study was registered in the Australian New Zealand Clinical Trials Registry before it was initiated (ACTRN12619001417178). Cardiac patients over 18 years of age undergoing open thoracic surgery or thoracoscopy were included in the study. Patients undergoing emergency surgery, under 18 years of age, those with a known bleeding disorder, renal insufficiency, hepatic failure, or congestive heart failure were excluded from the study. If the patient had undergone more than one surgery, only the data of the first surgery were included in the study.

Demographic data, pre-operative and post-operative hemogram values, type of drugs, amount of transfused blood and blood products, and complications mortality rate were recorded during the surgery. In addition, other laboratory tests, type of surgery, frequency of re-exploration, duration of intensive care and hospital stay, and causes of death were recorded within the first 48 h following the surgery. The patients were divided into two different groups. The patients who received aspirin as part of their treatment and discontinued it 5 days prior to the surgery formed group discontinued. Those who underwent surgery while the aspirin treatment was continued were included in Group Continued. Low Molecular Weight Heparin treatment was started in the preoperative period in all patients whose aspirin treatment was discontinued.

Statistical Analysis

While evaluating the findings obtained in the study, statistical analyzes were performed using IBM SPSS Statistics 22. Numerical data with normal distribution were analyzed through the one-way ANOVA test, those without via the Kruskal-Wallis-H test. The data that were found to have normal distribution as a result of the examination of the paired groups were analyzed with the Independent Samples t-test and the ones that were not with the Mann–Whitney-U test. The results were evaluated at a confidence level of 95% and a significance level of $p<0.05$.

Results

Aged between 18 and 79 years (55.81±14.91 years), 101 patients were included in the study. A total of 101 patients over 18 years of age who had undergone thoracic surgery were included in statistical analysis. Lobectomy was performed in 46 patients (61%) diagnosed with lung cancer, wedge resection was performed in 20 patients (26%) and surgical removal of mesothelioma was performed in 10 patients (13%) in Group Discontinued. Lobectomy was performed in 12 patients (48%) diagnosed with lung cancer, wedge resection was performed in 9 patients (36%) and surgical removal of mesothelioma was performed in 4 patients (16%) in group continued. Of the patients participating in our study, 28 (27.7%) were female and 73 (72.3%) were male. It was observed that the demographic data of the patients in both groups in the study were similar (Table 1). Eleven (69%) of the complications observed were

Table 1. Demographic characteristics of the groups

Acetyl Salicylic Acid	Group discontinued (n=76)		Group continued (n=25)		p
	n	%	n	%	
Gender			4	16	0.211[k]
Female	24	32			
Male	52	68	21	84	
Age	52.57±15.27 (56.5)		65.68±7.89 (64)		0.001*[d]
BMI	27.57±5.48 (25.8)		27.33±4.81 (27)		0.816[d]
ASA	7	9	0	0	0.001*[k]
ASA1					
ASA2	67	88	18	72	
ASA3	2	3	7	28	
Complication	64	84	21	84	0.98[k]
No					
Yes	12	16	4	16	

[k]: Chi-square test: values are given as frequency (percentage); [d]: Mann-Whitney U test: values are given as mean±standard deviation (median); *: p<0.05 Statistically significant difference between groups. BMI: Body mass index; ASA: American society of anesthesiologists.

pulmonary embolism (Fig. 1). It was observed in 9 patients (11.8%) in group discontinued and 2 patients (8%) in group continued. Three of the patients (19%) underwent surgical re-exploration. It was performed in 2 patients (2.6%) in group discontinued and 1 patient (4%) in group continued. Gastrointestinal system bleeding developed in 1 (4%) of the patients in group continued. DVT was observed in the upper extremity of 1 (1.3%) patient in group continued (Fig. 2). No mortality was observed.

A statistically significant difference was observed between the hemoglobin (Hb), Platelet, creatinine, and INR values of different surgical groups before and after the surgery (Table 2). Post-operative Hb value was statistically significantly lower in those who underwent mesothelioma surgery compared to the other groups (Table 2).

The duration of anesthesia, duration of surgery, and hospital stay were found to be similar between the patient groups included in the study. While the length of stay in the intensive care unit (ICU) was 0.08±0.27 days in group discontinued, it was 0.84±2.06 days in group continued (p=0.001, Table 3). When the groups were compared in terms of drainage times, no statistically significant difference was observed in the 24th h and total drainage amount. The amount of perioperative bleeding was found to be significantly higher in group continued than in group discontinued (610.8±695.1 vs. 292.63±356.35, p=0.003, Table 3). When the perioperative and postoperative uses of erythrocyte suspension and fresh frozen plasma were compared between the groups, no statistically significant difference was found (p>0.05, Table 4).

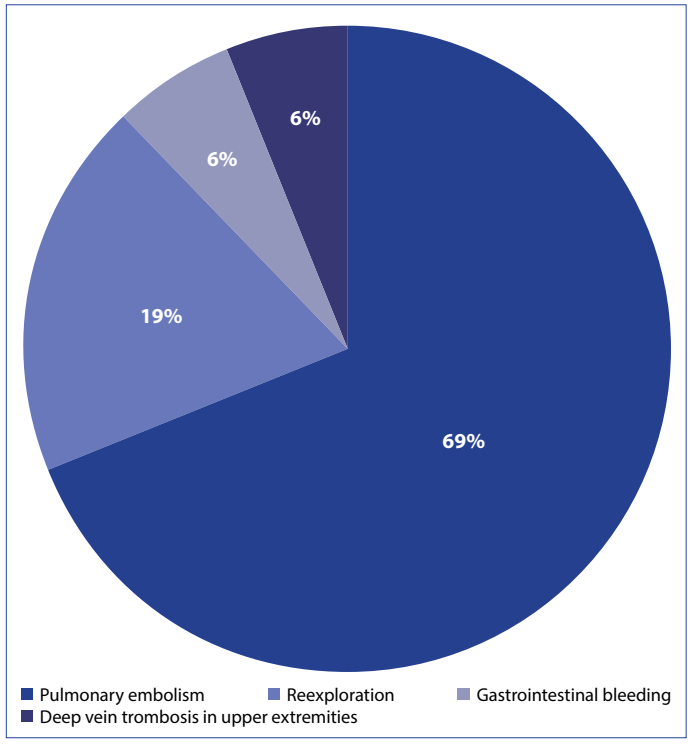

Figure 1. Distribution of complications among patients.

Discussion

In this prospective, observational cohort study, the patients who had undergone major thoracic surgery were compared based on whether they discontinued aspirin therapy. Although the total amount of bleeding was higher in the patients whose aspirin treatment was not discontinued, no significant difference was found when

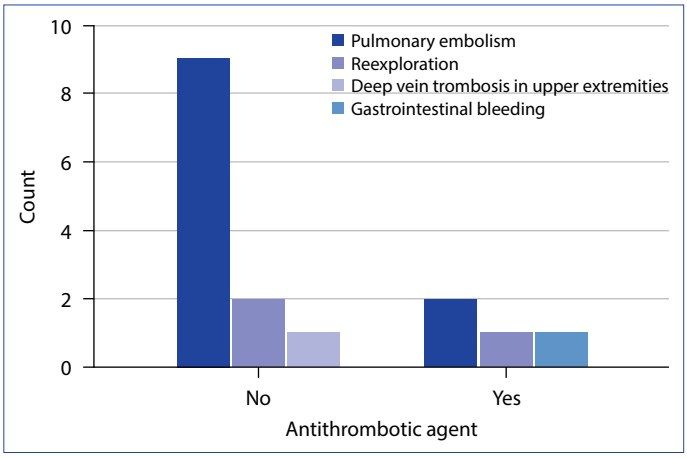

Figure 2. Box plot of post-operative visual analog scale scores.

the total use of blood and blood products was compared. While the length of hospital stay did not change in the patients whose aspirin treatment was not discontinued, it was found that the total length of their stay in the ICU was prolonged. The rate of pulmonary embolism and deep vein trombosis increased significantly in the patients whose treatment was interrupted.

Previously, aspirin used to be included in the therapy for the primary prevention of cardiovascular events. However, there have been some doubts regarding the use of aspirin for primary prevention in recent years.[8] The benefits of aspirin administration have been debated due to the increased risk of perioperative bleeding.[9] Observed especially during surgical procedures, hemorrhagic complications could sometimes be fatal. On the other hand, cardiac and pulmonary complications developing after surgery could also be fatal. Thoracic surgical operations are the ones where even massive bleeding might occur. Although they are frequently performed thoracoscopically, open surgery may be required.

A limited number of studies have been conducted on discontinuing the use of acetyl salicylic acid in patients undergoing thoracic surgery. There are striking findings regarding this issue that has been obtained from some studies in other surgical disciplines in the literature. However, the results of these studies are contradictory. In a study conducted with 214 colorectal cancer patients who underwent laparoscopic resection surgery, 89 of them were taken to surgery while their antiplatelet treatment was continued, and 125 were taken to surgery after their treatment was stopped.[10] In this study, no significant difference was found between the groups in terms of patient outcomes and risk of complications. Ullmann et al.[11] investigated the results of antiplatelet discontinuation in patients undergoing craniotomy and reported that it did not significantly affect the amount of postoperative bleeding. Our study discovered that the amount of perioperative bleeding in patients whose acetylsalicylic acid treatment was not discontinued increased approximately twice. However, this increase did not cause adverse effects on patient outcomes. A significant increase in the use of RBC and FFP was not recorded either.

The POISE-2 trial showed that perioperative use of aspirin in patients undergoing non-cardiac surgery increased the risk of major bleeding and did not decrease the rate of myocardial infarction.[12] Yu et al.[13] found that the bleeding risk increased due to the termination of antiplatelet agents in patients who had undergone thoracic surgery; however, no change was found regarding thrombotic complications due to the small sample size. In our study, pulmonary embolism occurred in nine patients in whom aspirin was discontinued in the preoperative period. It was observed in only two patients who were operated on under aspirin treatment. Thoracic surgery is a branch susceptible to major complications. These include prolonged pneumonia,

Table 2. Comparison of pre-operative and post-operative Hb, platelet, creatinine, and INR values of the patients who underwent lobectomy, wedge resection, and mesothelioma surgery

Acetyl Salicylic Acid	Lobectomy (n=58)	Wedge (n=29)	Mesothelioma (n=14)	p
Pre-operative Hb	13.67±1.8	14.1±1.49	12.46±1.83	0.016*[a]
Pre-operative Plt	271017±87691 (260000)	265069±96578 (233000)	346786±128180 (318500)	0.042*[b]
Pre-operative Cre	0.92±0.30 (0.82)	3.97±0.21 (1.03)	0.80±0.24 (0.73)	0.023*[b]
Pre-operative INR	0.99±0.15 (1)	0.90±0.18 (0.89)	1.17±0.72 (1)	0.040*[b]
Post-operative Hb	11.34±1.87	12.29±2	9.98±1.92	0.001*[a]
Post-operative Plt	290897±137561 (263000)	263586±132606 (222000)	261000±106049 (228500)	0.545[b]
Post-operative Cre	0.75±0.21 (0.71)	0.81±0.35 (0.75)	0.86±0.53 (0.74)	0.929[b]
Post-operative INR	1.11±0.12 (1.09)	1.07±0.07 (1.09)	1.18±0.19 (1.11)	0.276[b]

[a]: One-way ANOVA test: Values are given as mean±standard deviation; [b]: Kruskal-Wallis H test: Values are given as mean±standard deviation (median); *: p<0.05 Statistically significant difference between groups. Hb: Hemoglobin; Plt: Platelet; Cre: Creatinine; INR: International normalized ratio.

Table 3. Comparison of the groups in duration of anesthesia and surgery, amount of post-operative drainage, duration of intensive care and hospital stay, and perioperative bleeding

Acetyl Salicylic Acid	Group discontinued (n=76)	Group continued (n=25)	p
Duration of anesthesia (min)	247.76±88.28	270.20±113.56	0.603[d]
Duration of surgery (min)	200.07±83.98	221.20±103.18	0.495[d]
24th h drainage (ml)	306.58±145.45	418±293.64	0.087[d]
Total drainage (ml)	1021.71±488.08	1250±670.51	0.069[c]
Drain removal time (hour)	5.84±3.55	6.36±3.48	0.523[d]
ICU stay (day)	0.08±0.27	0.84±2.06	0.001*[d]
Hospital stay (day)	7.95±4.81	8±3.52	0.544[d]
Perioperative bleeding	292.63±356.35	610.8±695.1	0.003*[d]

[d]: Mann-Whitney U test: Values are given as mean±standard deviation (median); [c]: Independent samples t-test: Values are given as mean±standard deviation; *: p<0.05 statistically significant difference between groups; min: Minute; ml: Milliliter; ICU: Intensive care unit.

Table 4. Comparison of perioperative and post-operative use of erythrocyte suspension and fresh frozen plasma between the groups

Acetyl Salicylic Acid	Group discontinued (n=76)	Group continued (n=25)	p
Peroperative FFP	0.07±0.38 (0)	0.12±0.6 (0)	0.972[d]
Peroperative RBC	0.07±0.34 (0)	0.28±1.4 (0)	0.963[d]
FFP at ward	0.05±0.28 (0)	0.04±0.2 (0)	1.0[d]
RBC at ward	0.28±0.87 (0)	0.44±0.87 (0)	0.200[d]

[d]: Mann-Whitney U test: Values are given as mean±standard deviation (median). FFP: Fresh frozen plasma; RBC: Packed red blood cells.

atrial arrhythmias, and renal failure.[14] When these serious complications are accompanied by thrombotic complications such as pulmonary embolism or DVT, the outcome can be fatal.

Due to the aging of our population, the number of patients treated with platelet inhibitors as primary or secondary thromboembolic prophylaxis is increasing.[15] There are studies reporting a shorter hospital stay thanks to the use of perioperative aspirin.[16] Unlike this finding, no difference was found in the length of hospital stay in our study. However, a slight increase in the length of ICU stay was found in the patients in whom aspirin treatment was continued. The length of ICU stay is affected by many factors including diseases of the cardiovascular system, nervous system, and cerebrovascular system.[17]

Limitations

One of the most important limitations of this study is that major thoracic surgical operations were performed by open or thoracoscopic method. Differences in bleeding rate and complication risk can be observed in laparoscopic surgeries. Another limitation is that only the results of aspirin out of antithrombotic agents were analyzed. Further studies with large sample sizes investigating the effects of other anticoagulant agents are needed.

Conclusion

We found an increased risk of pulmonary embolism and deep vein thrombosis and a slightly prolonged ICU stay for the patients undergoing thoracic surgery with aspirin treatment was discontinued. It was concluded that pre-operative planning of anticoagulant treatment combined with current, evidence-based data with individual treatment modalities may positively effect on patient outcome.

Disclosures

Ethics Committee Approval: The study was approved by The Marmara University Faculty of Medicine Clinical Research Ethics Committee (Date: 02/02/2018, No: 09.2018.140).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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Authorship Contributions: Concept – A.S., E.Ş.; Design – A.S., M.Y., Z.A.; Supervision – A.S., Z.A.; Fundings – G.Ç., E.Ş.; Materials – G.Ç., O.E.; Data collection &/or processing – A.S., O.E.; Analysis and/or interpretation – T.L., E.S.; Literature search – O.E., T.L.; Writing – A.S., T.L.; Critical review – A.S., M.Y.

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