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석사학위 논문

아스피린 투여를 7일 이상 중단함 에도 불구하고 연장된 PFA-100 검 사값에 영향을 미치는 요소

조선대학교 대학원 의 학 과 조 동 원



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Factors associated with prolonged value of PFA-100 test, despite of aspirin discontinuation more than 7 days



조선대학교 대학원 의 학 과

조 동 원



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지도교수 유 병 식

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조선대학교 대학원

- 의 학 과
- 조 동 원



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위원장		조선대학교	교수	임경준	(인)
위	원	조선대학교	교수	김상훈	(인)
위	원	조선대학교	교수	유병식	(인)

조선대학교 대학원

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Contents

List of tables	i	i
Korean abstract	······ii	i

Ι.	Introduction1
11.	Methods ······3
III .	Results5
IV.	Discussion ······6

[References]	 12



List of Tables

Table	1	Baseline	characteristi	cs of	the	studv	population	
Tabic		Dascrinc		00 01		Study	population.	0

Tab	le 2	2.	Una	djus	sted	0dd	Rat i	0S	for	factor	S	associated	with	prol	onged	C/Epi
CT \	/alı	Je	••••	•••••	••••	•••••	••••	••••			• • •				••••••	11



국 문 초 록

아스피린 투여를 7일 이상 중단함에도 불구하고 연장된

PFA-100 검사값에 영향을 미치는 요소

조 동 원 지도교수 : 유 병 식 의 학 과 조선대학교 대학원

배경 : 정규수술을 앞둔, 아스피린을 투여중인 환자는 출혈의 위험성이 아스피 린을 중단함으로써 발생하는 심혈관계 합병증에 대한 위험성과 비슷하거나 더 큰 경우 수술 7일 전 중단하는 것이 추천되고 있는데, 일부 환자에서 아스피린 투여를 7일 이상 중단한 경우에도 PFA-100 검사값 중 Collagen/Epinephrine closure time (C/Epi CT)이 증가한 것이 종종 관찰된다. 이에 본 연구는 아스피 린 투여를 7일 이상 중단하였음에도 C/Epi CT을 연장시킬 수 있는 인자에 대해 서 알아보고자 하였다.

방법 : 정규수술을 위해 아스피린 투여를 7일 이상 중단한 환자를 대상으로 다 음과 같이 두 군으로 나누어 후향적으로 분석하였다. [제1군 : C/Epi CT이 정상 (197초 미만), 제2군 : C/Epi CT이 연장 (197초 이상)]

환자의 나이, 성별, 고혈압, 당뇨, 간염, 갑상샘 질환, 뇌경색, 뇌출혈, 치 매, 심혈관계 질환의 과거력, 적혈구용적, 혈소판수, 콜레스테롤 수치, 혈액형, 체질량 지수를 C/Epi CT의 연장과 연관된 인자로 선택하여 분석하였다.

결과 : 총 환자는 309명으로 제1군 (n = 226)과 비교하여 제2군 (n = 83)에서 성별과 혈액형이 유의한 차이를 보였다 (P=0.040 and 0.021). 남성과 비교하여 여성에서 C/Epi CT값의 연장에 대한 교차비는 1.769 (신뢰구간 1.056-2.96)이 고, 다른 혈액형과 비교하여 혈액형 0형의 교차비는 1.995 (신뢰구간 1.160-3.430)였다.

결론 : 아스피린 투여를 7일 이상 중단한 환자에서 C/Epi CT값의 연장은 여성,



혈액형 0형과 연관이 있음을 확인하였다.



Introduction

As the entry to an aging society, cardiovascular and cerebrovascular diseases are increased [1]. The use of antiplatelet agent is increasing because of its effectiveness in treatment and prevention of cardiovascular and cerebrovascular diseases [2]. Although taking aspirin is not a contraindication of regional anesthesia and neuraxial block, discontinuing of aspirin for a certain period can be recommended in some cases of surgeries to reduce the possibility of increased bleeding and hematoma, especially when the known bleeding risk is similar or more severe than the observed cardiovascular risk of aspirin withdrawal [3, 4, 5]. In some cases, epidural or intrathecal hematoma can be developed even the patients stopped medication of anticoagulant according to the recommendation of guidelines [4, 12]. And there is also the possibility of development of hemorrhagic complication such as subdural hematoma in patient without coagulation abnormalities in conventional laboratory tests [12].

In a case of aspirin, it is recommended to discontinue 7 days prior to surgery to allow active platelets to be present in the circulation [6]. In the previous study, optimal preoperative cessation period of aspirin was 7 days to recover platelet function according to the platelet function test[8].

Platelet function test can be a tool to evaluate the effect of aspirin discontinuation [7]. Platelet Function Analyzer-100 (Siemens, Eschborn, Germany, PFA-100) is helpful to diagnose hemostatic disorders with measuring Collagen/Epinephrine closure time (C/Epi CT) and Collagen/adenosine diphosphate closure time (C/ADP CT) [11]. Especially, C/Epi CT is very useful to examine the anti-platelet action of aspirin [7]. Thus, fast and accurate platelet function test like PFA-100 test can be a valuable tool to evaluate the risk of intraoperative bleeding before



surgery or hemorrhagic complications before a neuraxial block [13-15].

However, in some patients, C/Epi CT does not return to normal value even if aspirin has discontinued for more than 7 days. There is no large clinical trials about C/Epi CT changes after discontinuation of aspirin more 7 days, and little is known about the factors associated with continuous prolongation of C/Epi CT value.

The purpose of this study was to investigate the clinical factors of prolonged C/Epi CT despite of discontinuation of aspirin more than 7 days.



Methods

This study was retrospectively analyzed after approval of Institutional Review Board of Chosun university hospital. The patients who were taking aspirin and underwent the PFA-100 test (C/Epi CT) were included as subjects within the patient who underwent elective surgery from July 2010 to November 2014. Patients taking other antiplatelet agents with aspirin, with uncertain history of aspirin mediacation or unclear discontinuation period of aspirin, continued medication of aspirin, and with known coagulation disorders were excluded.

An enrolled patients were allocated into two groups. The patients, who had less than 197 seconds of C/Epi CT value, were assigned group 1. The patients, who had not less than 197 seconds of C/Epi CT value, were assigned group 2.

We recorded the demographic data [age, sex, body mass index (BMI)], the underlying diseases (hypertension, diabetes, hepatitis, thyroid disease, cerebral infarction, cerebral hemorrhage, dementia, cardiovascular disease), and the hemotologic results [hematocrit (Hct), platelet count (PC), total cholesterol level, blood type]. Continuous variables were converted as categorical variables as follows : age > 55, obesity (BMI > 23), low hematocrit (Hct < 38% in female, < 42% in male), low platelet (PC < 150,000/uL), low cholesterol (total cholesterol < 120 mg/dL).

Statistical analysis was done with SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA). Pearson's chi-squared test was done as the univariate analysis independence for categorical or binary covariates (age, sex, hypertension, diabetes, thyroid disease, cardiovascular disease, and blood type, obesity, low hematocrit, low platelet, low cholesterol). Fisher's exact test was used for hepatitis, cerebral infarction, cerebral hemorrhage, and dementia.



P value less than 0.05 was determined as statistically significant. When the value showed significant differences, odds ratio was calculated to figure out the clinical factors of prolonged C/Epi CT values.



Results

A total of 309 patients were selected as subjects and divided into two groups [Group 1 (n = 226), group 2 (n = 83)]. Baseline characteristics of the study population are presented in table 1.

Among the past history values, sex and blood type showed significant differences between two groups (P=0.040 and 0.021, Table 2).

Odds ratio of each value were analyzed. Female and blood type 0 were statistically significant (Table 2). In patients who discontinued aspirin more than 7 days, an estimated odd ratio for prolonged C/Epi CT value for female versus male was 1.769 (confidence interval, CI: 1.056-2.96) and an estimated odd ratio for prolonged C/Epi CT value for blood type 0 versus other blood types was 1.995 (CI: 1.160-3.430).



Discussion

This study was attempted to analyze the clinical factors of prolonged C/Epi CT value in patients who discontinued aspirin more than 7 days. In this study, it is showed that female and blood type 0 are the significant factors associated with prolonged C/Epi CT value despite of aspirin discontinuation more than 7 days.

There are some known factors that elongate PFA-100 values such as sex, age, oral contraceptives, pregnancy, von-Willebrand factor (vWF), blood types, metabolic syndromes, cardiovascular and cerebrovascular diseases, and liver diseases [11, 16-19]. However, these reports were the results from quantifying normal results from volunteers.

There was no study about factors about prolonged C/Epi CT value in patients who discontinued aspirin according to the guidelines. Thus, we started this study to find out the clinical factors of prolonged C/Epi CT value, despite the stopping aspirin for more than 7 days.

We observed the past histories of age, sex, hypertension, diabetes, hepatitis, thyroid disease, cerebral infarction, cerebral hemorrhage, dementia, cardiovascular disease, Hct, PC, total cholesterol level, blood type, and BMI. We thought histories of chronic disease such as hypertension, diabetes, hepatitis, cerebral infarction or hemorrhage, or cardiovascular disease could be the significant factors that increasing C/Epi CT value, because patients with these disease has a possibility of taking antiplatelet drugs for a long time[1, 2]. And we also thought cholesterol level and BMI could be the factor because metabolic diseases showed significant relationships with PFA-100 values [16]. However, there were no significant relationships between prolonged C/Epi CT value and chronic diseases, cholesterol level, or BMI.

Because PFA-100 value itself represents function of platelets, PC can be



a significant factor that affecting the results of C/Epi CT value. In facts, C/Epi CT values tends to be prolonged but the C/ADP CT value is usually normal in patients with medication of aspirin [11]. However, there were also no significant relationships between prolonged C/Epi CT value and PC. It seems that factors which is associated with platelet itself can not affect the results of C/Epi CT value if aspirin has discontinued more than 7 days because the lifetime of platelet is about 8 to 10 days[20].

However, female gender and blood type 0 were the significant clinical factors of prolonged C/Epi CT value. These results were in accordance with previous study that conducted to the normal patients that did not medicated aspirin[21]. It seems that prolongation of C/Epi CT value after discontinuation of aspirin more than 7 days is not associated with platelet itself but with other factors such as vWF. Blood type 0 are known to have significant correlation with prolonged C/Epi CT because patients of blood type 0 have lower vWF than patients of any other blood types[22]. It is reasonable because vWF plays important role in platelet aggregation and adhesion [23]. However, vWF cannot explain why female showed prolonged C/Epi CT value because there are no differences in plasma levels of vWF according to the sex[24]. Further evaluation should be done because it cannot be convinced that correlation with female and prolonged C/Epi CT value in this study is the result of biologic differences [21].

There are several limitations in this study. First, this study is non-randomized, retrospective clinical trial. Although we tried to rule out missing data for increasing precision, possibility of error cannot be excluded. Second, Since there are only two significant variables, multiple regression analysis was not performed. And logistic regression could not be done because no variables retained in model. In addition we did not show whether prolonged C/Epi CT value is actually associated with increase of surgical bleeding or increased risk of hematoma in spinal or epidural



anesthesia.

In conclusion, even though aspirin medication is discontinued more than 7 days before surgery, anesthesiologists should keep in mind that female, blood type 0, or both patients may have abnormal platelet function, and can lead to unexpected surgical bleeding or postoperative hematoma. In addition, we suggest that further evaluation is needed whether the prolonged C/Epi CT value clinically correlate with perioperative bleeding or hematoma.



Variables	Values, n (%)
Gender Male	147 (47.6)
Female	162 (52.4)
Age (y), mean (range)	64.6 (35-87)
Age > 55	250 (80.9)
Age ≤ 55	59 (19.1)
BMI, mean (range)	24.9 (16.2-34.2)
BMI > 23(obesity)	231 (72.9)
BMI ≤ 23	78 (24.6)
Hypertension	
Yes	254 (82.2)
No	55 (17.8)
Diabetes	
Yes	86 (27.8)
No	223 (72.2)
Hepatitis	
Yes	9 (2.9)
No	300 (97.1)
Thyroid disease	
Yes	27 (8.7)
No	282 (91.3)
Cerebral infarction	
Yes	18 (5.8)
No	291 (94.2)
Cerebral hemorrhage	
Yes	4 (1.3)
No	305 (98.7)
Dementia	
Yes	4 (1.3)
No	305 (98.7)
Cardiovascular disease	
Yes	34 (11)
No	275 (89)

Table 1. Baseline characteristics of the study population



Hematocrit, mean (range)	39.3 (27.5-52.1)				
Normal	149 (47)				
Low (< 38 in female, < 42 in male)	160 (50.5)				
Platelet (x 1,000/uL), mean (range)	273.1 (78-560)				
Normal	290 (91.5)				
Low (< 150,000)	19 (6.0)				
Total cholesterol(mg/dL), mean (range)	179.3 (61-334)				
Normal	287 (90.5)				
Low (< 120)	22 (6.9)				
Blood type					
0	83 (26.9)				
Non-O (A, B, AB)	226 (73.1)				



	Group1	Group2	Odds	05% CI	Р
	(n=226)	(n=83)	ratio	9376 CI	value
Female	110 (48.7%)	52 (62.7%)	1.769	1.056-2.96	0.029
Age > 55 (year)	181 (80.1%)	69 (83.1%)	1.225	0.633-2.373	0.546
Low Hematocrit ^a	118 (52.2%)	42 (50.6%)	0.938	0.567-1.551	0.802
Low Platelet ^b	15 (6.6%)	4 (4.8%)	0.712	0.229-2.211	0.555
Low Cholesterol ^c	18 (8%)	4 (4.8%)	0.585	0.192-1.782	0.341
Blood type O	21 (23%)	31 (37.3%)	1.995	1.160-3.430	0.012
Hypertension	181 (80.1%)	73 (88%)	1.815	0.868-3.793	0.109
Diabetes mellitus	68 (30.1%)	18 (21.7%)	0.643	0.355-1.166	0.144
Thyroid disease	17 (7.5%)	10 (12%)	1.684	0.738-3.844	0.212
Hepatitis	7 (3.1%)	2 (2.4%)	0.772	0.157-3.796	0.950
Cerebral infartion	16 (7.1%)	2 (2.4%)	0.324	0.073-1.441	0.201
Cerebral hemorrhage	2 (0.9%)	2 (2.4%)	2.765	0.383-19.957	0.629
Dementia	1 (0.4%)	3 (3.6%)	8.438	0.865-82.285	0.106
Cardiovascular disease ^d	29 (12.8%)	5 (6%)	0.435	0.163-1.166	0.090
Obesity ^e	168 (74.3%)	63 (75.9%)	1.088	0.606-1.952	0.779

Table 2. Unadjusted Odd Ratios for factors associated with prolonged C/Epi CT value

Values are expressed as numbers of patients (%). Group 1, normal PFA value (<197 seconds); Group 2, prolonged PFA value (≥197 seconds); CI, confidence interval; C/Epi CT, Collagen/Epinephrine closure time; BMI, body mass index. P<0.05 considered as statistically significant. a: Low hematocrit means lower than 38% in woman, 42% in man. b: Low platelet means lower than 150,000. c: Low cholesterol means lower than 120 mg/dL. d: Cardiovascular disease means angina history or myocardial infarction history. e: Obesity means over BMI 23.



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