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외과학 석사 학위논문

수술 전 항혈소판 및 항응고제
치료를 받은 환자의 위암 수술 후
주요 출혈 위험성 연구

2020 년 2 월

서울대학교 대학원

의학과 외과학

임차미

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Postoperative major bleeding risk of gastrectomy for
gastric cancer in preoperative anticoagulant or
antiplatelet agents treatment patients.

지도교수 김형호

이 논문을 외과학 석사 학위논문으로 제출함

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Abstract

Postoperative major bleeding risk of gastrectomy for gastric cancer in preoperative anticoagulant or antiplatelet agents treatment patients.

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Background: Antiplatelets and anticoagulants are widely adopted in everyday clinical practice. Postoperative major bleeding is rare but may cause fatal complications in patients who underwent gastric cancer surgery. We investigated association of antiplatelets and anticoagulants with postoperative major bleeding risk.

Methods: The study populations consisted of patients over 18 years of age who were admitted to Seoul National University Bundang Hospital (SNUBH) between January 2012 and December 2017 for gastric cancer surgery. The primary outcome was postoperative major bleeding which was defined

as intraluminal bleeding or intraabdominal bleeding with fall in hemoglobin level of at least 2 g/dL (1.24 mmol/L), or transfusion, of at least two units of red blood cells (RBCs), with temporal association within 24 h to the bleeding. The secondary outcomes were intraoperative, postoperative transfusion and early complication rate.

Results: Postoperative major bleeding were 11 (2.0%) cases in antiplatelets/anticoagulants group and 43 (1.3%) in control group ($P = 0.234$). Intraoperative and postoperative transfusion rate were significantly higher in antiplatelets/anticoagulants group than control group [168 (4.9%) vs. 59 (10.5%); $P < 0.001$ and 174 (5.1%) vs. 47 (8.3%); $P = 0.003$]. Early complication developed in 73 (13%) patients in antiplatelets/anticoagulants group and 364 (10.7 %) patients in control group ($P = 0.109$). In multivariable analysis, male [odds ratio (OR) : 2.623, 95% confidence interval (CI) : 1.267–5.429 ; $P = 0.009$] and advanced stage (III, IV) [OR : 2.869, 95% CI : 1.398–5.889 ; $P = 0.004$] were independent significant risk factors for postoperative major bleeding

Conclusions: Preoperative antiplatelets or anticoagulants administration didn't increase the risk of postoperative major bleeding after gastric cancer surgery significantly. Male and

advanced stage (III, IV) were the independent risk factors for postoperative major bleeding risk regardless of antiplatelets or anticoagulants.

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Keywords: Antiplatelets; Anticoagulants; Gastric cancer surgery; Complications; Hemorrhage; Thromboembolism

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Introduction

Antiplateletss and anticoagulants are widely adopted into everyday clinical practice. Aspirin is an anti-inflammatory and antiplatelet agent whose effect is mediated through irreversible inhibition of cyclooxygenase 1 and 2 (COX1 and COX2). The Adenosine diphosphate (ADP) receptor blockers inhibit platelet aggregation by preventing the binding of ADP to its specific platelet receptor. Newer agents (clopidogrel, prasugrel, and ticagrelor) are routinely prescribed as part of a dual antiplatelet therapy (DAPT) regimen in patients with ischemic heart disease (1). Aspirin and clopidogrel are most common agents in cardiovascular disease for primary and secondary prevention (2). Warfarin was used for prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism (PE). In additions, it could be adopted for prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and cardiac valve replacement. Recently, non-Vitamin K antagonist oral anticoagulants (NOAC) are used in patients with non-valvular atrial fibrillation (AF) and for the treatment and prevention of venous thromboembolism (3). The use of these agents are increasing, surgeons encounter the patients who are

on antiplatelet or anticoagulant therapy during perioperative periods (4).

Postoperative major bleeding is rare but may cause fatal complications in patients who underwent gastric cancer surgery. In a literature, the estimated rate of hemorrhagic complications following gastrectomy is 0.9% (in a series of more than 1500 patients), with a mortality rate of 20%. Endovascular treatment, performed as first-line treatment in 80% of cases, is associated with a success rate of 80% (5). Surgical site major bleeding is unexpected and cause hemodynamic instability (6). Rapid second interventions; transfusions, endoscopic coagulation, radiologic intervention or explorative laparotomy are needed. Therefore, investigating postoperative major bleeding risk in patients who are using antiplatelets or anticoagulation is critical for surgery.

However, there are controversies regarding the association between antiplatelets or anticoagulants use and risk of major bleeding risk (7) (8) (9) (10). Therefore, we investigated association of antiplatelet agents or anticoagulants and postoperative major bleeding risk after gastric cancer surgery.

Methods

Design and ethical statement

This study is based on retrospective analysis. It was approved by the institutional review board (IRB) of Seoul National University Bundang Hospital (SNUBH; single tertiary academic hospital) (IRB approval number: B-1907-552-1004). Informed consent was waived due to the retrospective study design which analyzes the health records of patients who had already completed their treatment. We followed the Strengthening the Reporting of Observational Studies in The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting on observational cohort studies.

Patient selection

The study populations consisted of patients over 18 years of age who were admitted to SNUBH between January 2012 and December 2017 for gastric cancer surgery. We only include patients who underwent radical curative gastric resection. Palliative operations, gastrectomy with other surgery at the

same time, and all emergency surgeries were excluded from the analysis.

Data collection

We obtained data from the electronic medical records of all patients, stored in the Bundang Hospital Electronic System for Total Care (BESTCare) at SNUBH for this study (11). We collected the data of physical characteristics (sex, age [years], body mass index [BMI, kgm^{-2}]), American Society of Anesthesiologists (ASA) classification, comorbidity, TMN stage, surgery type, combined resections, lymphadenectomy, operation time, hospital day, and postoperative intensive care unit (ICU) care.

Surgical technique

A standard radical gastrectomy with D1+ or D2 lymph node dissection was performed in gastric cancer surgery according to the Japanese Gastric treatment guidelines (12). Pylorus-preserving gastrectomy (PPG), proximal gastrectomy (PG) or segmental resections were performed in cT1cN0

tumors. Meticulous hemostasis with topical hemostatic agents was performed in surgical procedures.

Outcome measure

The primary outcome was postoperative major bleeding which was defined as intraluminal bleeding or intraabdominal bleeding with fall in hemoglobin level of at least 2 g/dL (1.24 mmol/L), or transfusion, indicated by the bleeding, of at least two units of RBCs, with temporal association within 24 h to the surgery (6). Intraluminal bleeding was diagnosed by hematochezia, melena, hematemesis, or endoscopic findings. Intraabdominal bleeding was diagnosed by sanguineous Jackson–Pratt drains or hemoperitoneum, hematoma, or extravasation of contrast material on CT finding. Secondary outcome measures included intraoperative, postoperative transfusion, and early complication rates. Administration of RBCs during surgery was defined as intraoperative transfusion. If RBCs were transfused in 2 days after surgery, we considered it as postoperative transfusion. Early complication was defined as any deviation from the ideal postoperative course that is not inherent in the procedure and does not comprise a failure to cure (13) in postoperative 30–days. It was graded by Calvin–Dindo Classifications (14).

Statistical analysis

Baseline characteristics were presented as the mean value with standard deviation (SD) for continuous variables or number with percentage for the categorical variables. Categorical variables were compared using the Chi-square and Student's t test was used to compare continuous data. We performed a univariable and multivariable logistic regression to investigate the individual association of all covariates with postoperative major bleeding. All results of logistic regression model were provided as odds ratio (OR)s with 95% confidence interval (CI)s and goodness of fit in each multivariable model was confirmed by Hosmer-Lemeshow statistic test with a criterion of $P > 0.05$. There was no multi-collinearity issue in each multivariable model with variance inflation factor < 2.0 . All statistical analyses were performed using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient clinicopathologic findings

From January 2012 to December 2017, 4,322 patients were admitted for surgery associated with gastric cancer. According to the inclusion criteria, 3,980 adult patients were included in this cohort. 563 (14.1%) patients were on antiplatelets or anticoagulants therapy. 541 (96.1%) patients took antiplatelets and 34 (6.0%) patients were on anticoagulation. Aspirin (79.4%) was most commonly used, followed by clopidogrel (20.1%) and other antiplatelet agents (6.9%) (Table 2). Table 1 showed patient characteristics in each group. In antiplatelets/anticoagulants group, the proportion of male patients were higher [416 (73.9%) vs. 2198 (64.3%); $P < 0.001$] and mean age was older [69.04 (± 8.41) vs. 59.57 (± 12.48); $P < 0.001$] than control group. Body mass index (BMI) [23.70 (± 3.37) vs. 24.89 (± 3.68)], ASA score ≥ 2 [1883 (55.1%) vs. 544 (96.6%)], comorbidity [2307 (67.5%) vs. 562 (99.8%)], and postoperative ICU care [161 (4.7%) vs. 80 (14.2%)] were significantly different between two groups ($P < 0.001$). However, there were no significantly different in TNM stage,

surgery type, resection type, combined resection, lymphadenectomy, operation time, and days of hospital stay.

Outcomes

11 (2.0%) cases of postoperative major bleeding were observed in antiplatelets/anticoagulants group, which is not significantly different with control group [43 (1.3%); $P = 0.234$]. Intraoperative and postoperative transfusion rate were significantly higher in antiplatelets/anticoagulants group than control group [168 (4.9%) vs. 59 (10.5%); $P < 0.001$ and 174 (5.1%) vs. 47 (8.3%); $P = 0.003$]. Early complication developed in 73 (13%) patients in antiplatelets/anticoagulants group and (10.7 %) patients in control group ($P = 0.109$).

Risk factors for the postoperative major bleeding risk

Univariable and multivariable analyses for investigating risk factors for postoperative major bleeding were conducted. In univariable analysis, male, comorbidity, advanced stage (III, IV), open surgery, and total gastrectomy were associated with postoperative major bleeding. However, using multivariable

analysis, male [OR : 2.623, 95% CI, 1.267-5.429 ; $P = 0.009$]
and advanced stage (III, IV) [OR : 2.869, 95% CI : 1.398-5.889 ;
 $P = 0.004$] were independent significant risk factors for
postoperative major bleeding (Table 5).

Discussion

Overall, postoperative major bleeding rate was 1.35% for 6 years in 3,980 patients. Our study showed intraoperative and postoperative transfusion rate were significantly higher in patients with antiplatelets or anticoagulants. However, postoperative major bleeding risk was not increased in this group. Intraoperative hemorrhage is most commonly caused by structural defects, anticoagulant excess, hyperfibrinolysis, or a generalized and severe disorder of hemostasis, such as disseminated intravascular coagulation. Early postoperative hemorrhage (within 2 days of surgery) suggests a defect in primary hemostasis, such as significant thrombocytopenia (platelet count less than $50 \times 10^9 /L$) or platelet dysfunction, each of which may be inherited or acquired (15). Intraoperative and postoperative bleedings can be associated with medical problems of patients including administration of medications which affects coagulation cascade and platelet aggregation. Gonzalez-Rivas et al. pointed out experience deficit of the surgeon, difficult vascular dissection: fused artery or vein, calcified or malignant hilar lymph nodes, vascular injury with cautery or energy devices, vascular laceration by the

endostapler (limited angle or forced insertion), vascular injury on the posterior wall with a right-angled clamp or scissors, failure of staplers (especially when dealing with a thick fissure), laceration during blunt dissection, metal or polymer vascular clip loosening or misplacement, and excessive traction of fragile vessels (after chemotherapy, corticoid treatment or in elderly patients) as main causes of bleeding during thoracoscopic surgery (16). Postoperative life threatening bleeding can be associated with technical problem during the surgery. Although the patients have bleeding tendency, it can be controlled by meticulous surgical technique by experienced surgeons.

In multivariable analysis, male and advanced stage (III, IV) were revealed risk factors of postoperative major bleeding risk. Park et al. analyzed male was independent risk factor of postoperative hemorrhage following gastrectomy (17). In transoral surgery of the oropharynx, males were more likely than females to have a bleeding episode requiring operative intervention. They raised the possibility that it is unlikely to be related to anatomy or pathologic findings but could possibly be the result of increased postoperative exertion or activity (18). There is a literature that bleeding events were more frequent in males with atrial fibrillation during warfarin therapy (19). There are some literatures that bleeding events are more frequent in

advanced stage (5) (20) (21). To achieve a curative resection, metastatic lymph nodes and other organs that tumor cell invaded should be removed. During lymph node dissections, the high temperature of the ultrasonic knife may injure blood vessel walls and adjacent tissue, facilitating vascular damage and aneurysm formation, which can result in postoperative bleeding. Although over D2 lymphadenectomy and resection of other organs were not revealed as risk factors in multivariable analysis in this study, patients with advanced stage were usually in the high-risk group for postoperative major bleeding. In addition, Xie et al. showed that patients who suffered from postoperative gastrointestinal leakage have a 7 times higher likelihood of postoperative bleeding. During and after gastrectomy, the stomach is stressed and in inflammation state. Digestive juices seep into the abdominal cavity or anastomosis site and erode blood vessels, resulting in arterial rupture or aneurysm formation or anastomosis site bleeding (21).

We performed several subgroup analyses. First, in terms of duration of discontinuation, there was no definite correlation with bleeding risk. Before the surgery, we consulted to the cardiologists for duration of discontinue antiplatelet agents. The decision of cessation and resumption of antiplatelet agents are based on the risk stratification for thrombosis and bleeding.

According to the risk assessment, gastric cancer surgery is intermediate risk. Being in high risk of thrombosis, patients continue medications perioperative periods. However, they are in intermediate or low risk of perioperative thrombosis, physician recommend stop 5-7 days before the surgery (22). In this study, the median days of discontinuation was 7. However, 47% of patients followed their protocol strictly. There were various durations of discontinuation periods. The medications were discontinued arbitrarily for various reasons. Some patients underwent another procedure such as endoscopic biopsy, clipping, or coagulation a couple of weeks before elective surgery. The duration of discontinuance of antiplatelets or anticoagulants could be prolonged. Other patients stopped administration of antiplatelets because of lack of education and anxiety of bleeding. There was a gap between the physician's recommendation and the patient's actual behavior in real world. It could affect the result of this subgroup analysis. Second, we investigated postoperative major bleeding risk with antiplatelets/anticoagulants in laparoscopic surgery group. The result was similar with whole group. Postoperative major bleeding were not significantly different between two groups ($P = 0.123$). Intraoperative and postoperative transfusion rate were significantly higher in antiplatelets/anticoagulants group than

control group ($P < 0.001$ and $P = 0.004$, respectively). Early complication was not significantly different ($P = 0.109$) (Table 4). These results suggest that laparoscopic gastric cancer surgery can be safely performed in patient with antiplatelets or anticoagulants. Last, we analyzed postoperative major bleeding risk with antiplatelets/anticoagulants in advanced stage (III, IV) group. As mentioned above, advanced stage was an independent risk factor of postoperative major bleeding risk. In this subgroup analysis, postoperative major bleeding risk was not significantly increased in antiplatelets/anticoagulants group. This result support that the antiplatelets/anticoagulants use does not increase the postoperative major bleeding risk.

Based on retrospective design, the duration of discontinuation could not be controlled by protocol of our institution. For investigating accurate correlations between antiplatelets or anticoagulants with postoperative major bleeding, this variable should be controlled. To our best knowledge, it is the first study that the patients who took NOACs were included in antiPLTs or anticoagulants group. However, only 11 patients (2%) who use NOAC during perioperative periods were included in this study. The patients with NOAC have been undergone gastric cancer surgery from 2014 in our institute. The use of these agents are increasing, the further study needs to be

conducted for the association between NOAC and postoperative major bleeding.

In conclusion, preoperative antiplatelets or anticoagulants administration didn't increase the risk of postoperative major bleeding after gastric cancer surgery significantly. Male and advanced stage (III, IV) were the independent risk factors for postoperative major bleeding risk regardless of antiplatelets or anticoagulants.

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Tables

Table 1. Clinicopathological variables of patients

Variables	Control group (n=3417)	AntiPLTs/ anticoagulants group (n=563)	P value
Sex			<0.001
male	2198 (64.3)	416 (73.9)	
female	1219 (35.7)	147 (26.1)	
Age, yr	59.57 (\pm 12.48)	69.04 (\pm 8.41)	<0.001
BMI, kg m ⁻²	23.70 (\pm 3.37)	24.89 (\pm 3.68)	<0.001
ASA			<0.001
1	1534 (44.9)	19 (3.4)	
2	1773 (51.9)	449 (79.8)	
3	108 (3.2)	89 (15.8)	
4	2 (0.1)	5 (0.9)	
5	0 (0)	0 (0)	
6	0 (0)	1 (0.2)	
Comorbidity	2307 (67.5)	562 (99.8)	<0.001
TNM Stage			0.195
IA	1938 (56.7)	321 (56.9)	
IB	347 (10.2)	72 (12.8)	
IIA	261 (7.6)	32 (5.7)	
IIB	198 (5.8)	30 (5.3)	
IIIA	187 (5.5)	34 (6.0)	
IIIB	170 (5.0)	30 (5.3)	

IIIC	228 (6.7)	37 (6.6)	
IV	88 (2.6)	7 (1.2)	
Surgery type			0.867
Laparoscopy	3146 (92.1)	517 (91.8)	
Open	271 (7.9)	46 (8.2)	
Resection type			0.131
Distal gastrectomy	2423 (70.9)	406 (72.1)	
Total gastrectomy	580 (17)	90 (16)	
Proximal gastrectomy	178 (5.2)	39 (6.9)	
PPG	179 (5.2)	18 (3.2)	
Segmental resection	57 (1.7)	10 (1.8)	
Combined resection	382 (11.2)	63 (11.2)	1.000
Lymphadenectomy			0.111
D0	84 (2.5)	20 (3.5)	
D1	91 (2.7)	24 (4.3)	
D1+	1788 (52.3)	292 (51.8)	
D2	1380 (40.4)	220 (39.2)	
D2+	45 (1.3)	5 (0.9)	
D3	29 (0.8)	2 (0.4)	
Operation time, min	192.67 (\pm 66.17)	185.95 (\pm 67.78)	0.026
Hospital stay, day	6.97 (\pm 8.19)	7.63 (\pm 6.41)	0.090
Postoperative ICU care	161 (4.7)	80 (14.2)	<0.001

Presented as Number (percentage) or mean value (standard deviation)

PLT, platelet; BMI, body mass index; PPG, pylorus-preserving gastrectomy;

Table 2. Type of antiplatelets and anticoagulants

Variables	Number (n=563)	Percentage
Antiplatelets	541	96.1
Aspirin	448	79.4
Clopidogrel	113	20.1
Others	39	6.9
Dual antiplatelets	59	10.5
Anticoagulants	34	6.0
Warfarin	24	4.3
NOAC	11	2.0

NOAC, non-Vitamin K antagonist oral anticoagulants

Table 3. Postoperative complications

Variables	Control group (n=3417)	AntiPLTs/ anticoagulants group (n=563)	P value
Postoperative bleeding	43 (1.3)	11 (2.0)	0.234
Intraoperative transfusion	168 (4.9)	59 (10.5)	<0.001
Postoperative transfusion	174 (5.1)	47 (8.3)	0.003
Early complication	364 (10.7)	73 (13.0)	0.109

PLT, platelet

Table 4. Postoperative complications (Laparoscopy)

Variables	Control group (n=3146)	AntiPLTs/ anticoagulants group (n=517)	P value
Postoperative bleeding	34 (1.1)	10 (1.9)	0.123
Intraoperative transfusion	108 (3.4)	46 (8.9)	<0.001
Postoperative transfusion	120 (3.8)	35 (6.8)	0.004
Early complication	279 (8.9)	57 (11.0)	0.118

PLT, platelet

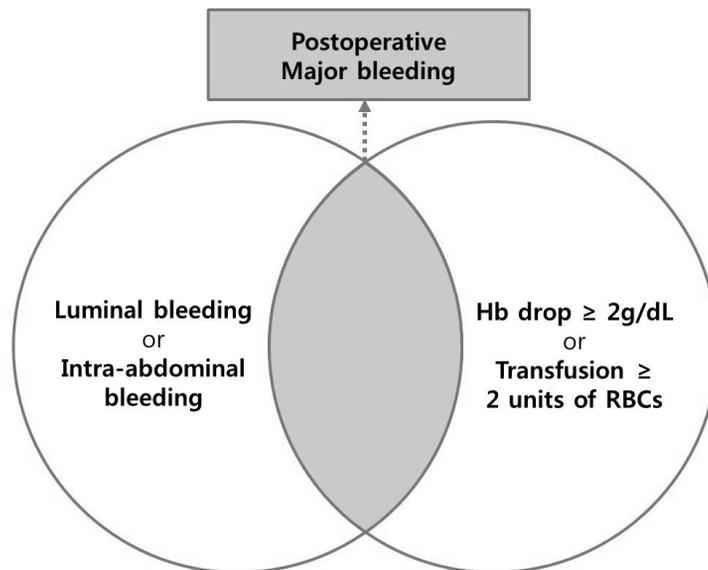
Table 5. Univariable analysis and multivariable analysis of postoperative bleeding complication

Variables	Univariable analysis			Multivariable analysis		
	OR	95 % CI	P value	OR	95 % CI	P value
Sex: male	2.614	1.287– 5.419	0.006	2.623	1.267– 5.429	0.009
Age < 40 or ≥70	1.490	0.865– 2.566	0.190	1.377	0.781– 2.427	0.269
BMI ≥ 25	1.125	0.645– 1.962	0.773	1.244	0.698– 2.215	0.459
ASA ≥ 2	1.530	0.850– 2.753	0.163	0.935	0.469– 1.866	0.850
AntiPLTs/ anticoagulants	1.564	0.801– 3.051	0.234	1.188	0.580– 2.433	0.637
Comorbidity	2.247	1.057– 4.775	0.032	1.808	0.768– 4.257	0.175
Advanced stage (III, IV)	3.122	1.760– 5.537	<0.001	2.869	1.398– 5.889	0.004
Laparoscopy	0.373	0.186– 0.749	0.009	0.591	0.267– 1.309	0.195
Total gastrectomy	2.107	1.168– 3.801	0.017	1.493	0.773– 2.882	0.233
Resection of other organs	1.389	0.65–2 .961	0.514	0.893	0.393– 2.027	0.786
Lymphadenectomy ≥ D2	1.095	0.638– 1.881	0.782	0.643	0.344– 1.203	0.167

PLT, platelet; OR, odds ratio; CI, confidence interval

Figures

Figure 1. Definition of postoperative major bleeding



국문초록

서론: 항혈소판제와 항응고제는 임상에서 넓게 사용되고 있다. 수술 후 주요 출혈은 위암수술을 받은 환자에게 발생할 수 있는 드물지만 치명적인 합병증이다.

방법: 연구대상은 2012년 1월부터 2017년 12월 까지 위암수술을 받기 위해 분당서울대병원에 입원한 18세 이상의 환자들이다. 주요 결과는 수술 후 주요 출혈로 하였고, 이는 장관 내 출혈이나 복강 내 출혈이 있으면서 혈색소가 적어도 2g/dL (1.24mmol/L) 감소하거나 출혈 후 24간 내에 적어도 두 개 이상의 적혈구 제제 수혈로 정의하였다. 이차 결과는 수술 중, 수술 후 수혈과 초기 합병증 비율로 하였다.

결과: 수술 후 주요 출혈은 항혈소판나 항응고제를 복용하는 군에서 11례 (2.0%), 대조군에서 43례 (1.3%) 발생하였다 ($P = 0.234$). 수술 중, 수술 후 수혈은 항혈소판나 항응고제를 복용하는 군에서 유의하게 많았다 ($P < 0.001$, $P = 0.003$). 초기 합병증은 두 군간에 유의한 차이가 없었다. 다변량 분석에서, 남성과 진행암 (병기 III, IV) 은 위암 수술 후 주요 출혈의 독립적인 위험 인자로 밝혀졌다.

결론: 수술 전 항혈소판제나 항응고제 투약은 위암 수술 후 주요 출혈 위험을 유의하게 높이지 않는다. 남성과 진행암 (병기 III, IV)은 항혈소판제나 항응고제 복용 여부와 관계없이 위암 수술 후 주요 출혈의 독립적인 위험 인자이다.

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주요어 : 항혈소판제; 항응고제; 위암 수술; 합병증; 출혈;
혈전색전증

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