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ORIGINAL ARTICLE

Association between preoperative use of antithrombotic medications and intraoperative transfusion in older patients undergoing cancer surgery

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Long-acting anticoagulants

Summary *Background:* Management of antiplatelet agents and other chronic anticoagulation medications in patients scheduled for surgery can reduce intraoperative bleeding complications. However, few studies on the association of antithrombotics, relative to their duration of action, with intraoperative transfusion have been conducted. We aimed to determine the association of recent use of antithrombotics, relative to their duration of action, with intraoperative transfusion in elderly people undergoing cancer surgery.
Methods: The study subjects were patients aged 65 years or older who were scheduled for cancer surgery and presented for comprehensive geriatric assessment. We reviewed the baseline patient characteristics obtained from electronic medical records and the patients' preoperative medication history, including anticoagulants, antiplatelet agents, and streptokinase/streptodornase.
Results: A total of 475 cancer patients were included. Multivariate analysis showed that long-acting anticoagulant therapy before surgery was a significant risk factor for intraoperative transfusion. Long-acting anticoagulants increased the risk of transfusion approximately 15.9-fold (95% CI 1.9–136.2). The attributable risk of long-acting anticoagulants to transfusion

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was approximately 93.7%. Also, low body mass index (BMI) and hepato-pancreato-biliary (HPB) surgery were significantly associated with intraoperative transfusion. The adjusted odds ratios for low BMI (<18.5 kg/m^2) and HPB surgery (reference: lower gastrointestinal surgery) were 5.3 (95% CI 1.8—15.4) and 4.9 (95% CI 1.9—12.5), respectively.
Conclusions: It was found that the perioperative use of long-acting anticoagulants was associated with an increased risk of intraoperative transfusion, further highlighting the importance of medication optimization for elderly patients with cancer surgery.

1. Introduction

It is common for elderly patients to suffer from one or more chronic diseases. Comorbid conditions may not only affect life expectancy but also complicate major surgery. Specifically, comorbidity can increase operative risk and complicate post-surgical management. Therefore, accurate prediction of surgical risk specific to this population is of great importance.

Among intraoperative complications, transfusion has been shown to be a risk factor for postoperative complications. Transfusion during surgery has been shown to increase the risk of postoperative fever, intra-abdominal abscess, and bleeding; also, it is an independent factor for postoperative morbidity, resulting in reoperation, readmission, length of hospital stay, and mortality.[1—4]

Patient-specific factors such as age, underlying disease, and surgical site have been identified as risk factors for intraoperative transfusion.[4,5] In addition, intraoperative management of anticoagulation including antiplatelet therapy has been suggested to reduce intraoperative bleeding complications.[4] However, few studies on the association of antithrombotics, relative to their duration of action, with intraoperative transfusion have been conducted. Therefore, we aimed to analyze the impact of antithrombotic therapy, according to drug half-life and duration of action, on intraoperative transfusion in oncology patients undergoing preoperative CGA.

2. Method

2.1. Study population and data collection

This study is a retrospective analysis of prospectively collected data. We included patients aged 65 years or older who were scheduled for cancer surgery and who underwent comprehensive geriatric assessment (CGA) before surgery at the Geriatric Center of Seoul National University Bundang Hospital from January 2014 to June 2015.[6] Patients with solid tumors who underwent all types of cancer surgery procedures were included, regardless of cancer stage. Patients who refused surgery or did not undergo cancer surgery were excluded.

Baseline characteristics of participants were collected from electronic medical records, including age, sex, body mass index (BMI), cancer type, and comorbidities. Serum creatinine, lean body weight, sex, and age were used to estimate renal function with the Cockcroft—Gault equation. Risk of delirium was measured using the Nursing Delirium Screening Scale with scores ranging from 0 to 5.[7]

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (the Seoul National University Bundang Hospital Institutional Review Board, B-1811-507-102) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

2.2. CGA of cognitive function and preoperative medication history

Preoperative CGA was performed using a tool established by a geriatrics team composed of geriatricians, nurse specialists, dietitians, and pharmacists. The pharmacists were responsible for medication reviews. Cognitive function was evaluated using the Korean version of the Mini-Mental Status Examination (MMSE-KC) with scores ranging from 0 to 30 (dementia score < 17).[8]

The medication reviews were performed as follows: 1) Patients were instructed to bring records of their prescriptions or the actual medications to the CGA, and 2) pharmacists interviewed the patients and their caregivers to clarify all prescription and non-prescription medications. Information on medications only taken as needed (PRN) was also obtained. The total number of medications per patient, preoperative discontinuation-requiring medications (PDRMs), and potentially inappropriate medications (PIMs) were analyzed.

PDRMs were defined as medications that should be discontinued before surgery due to surgical risks; they included antithrombotic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), and streptokinase/streptodornase, which pose risks of postoperative hemorrhage; metformin, due to the risk of lactic acidosis; exogenous hormones, due to the risk of venous thromboembolism; and herbal medications, due to uncertainty about their actual contents.[6] Antithrombotic medications were subclassified as short-acting and long-acting anticoagulants and short-acting and long-acting antiplatelet agents, according to their mechanism and duration of action.[9—13] Peripheral vasodilators that have antiplatelet activity were also included in the bleeding risk category (Table 1).[14—18]

Table 1 Preoperative medications reviewed during the comprehensive geriatric assessment.

Therapeutic Category	Medications
Potentially inappropriate medication	
Delirium risk	
Anticholinergics	
First-generation antihistamines	Chlorpheniramine, Hydroxyzine
Antispasmodics	Chlordiazepoxide, Scopolamine
Antipsychotics	Quetiapine
Benzodiazepines	
Short- and intermediate -acting	Alprazolam, Triazolam
Long-acting	Clonazepam, Diazepam
Chlorpromazine	
Corticosteroids	Prednisolone
H2-receptor antagonists	Cimetidine, Ranitidine
Sedative hypnotics	Zolpidem
Fall risk	
Anticonvulsants	Carbamazepine, Valproate
Antipsychotics	Chlorpromazine, Quetiapine
Benzodiazepines	
Short- and intermediate-acting	Alprazolam, Triazolam
Long-acting	Diazepam
Nonbenzodiazepine benzodiazepine receptor agonist hypnotics	Zolpidem
Tricyclic antidepressants	Amitriptyline, Imipramine
Selective serotonin reuptake inhibitors	Duloxetine, Paroxetine
Opioids	Fentanyl, Morphine
Preoperative discontinuation-requiring medications	
Bleeding risk	
Anticoagulant agents	
Short-acting	Dabigatran, Dalteparin, Rivaroxaban
Long-acting	Mesoglycan, Sulodexide, Warfarin
Antiplatelet agents	
Short-acting	Beraprost, Cilostazol, Indobufen, Sarpogrelate
Long-acting	Aspirin, Clopidogrel, Triflusal
NSAID	
Short-acting	Aceclofenac, Dexibuprofen, Ibuprofen, Loxoprofen, Mefenamic acid, Talniflumate
Long-acting	Celecoxib, Meloxicam, Naproxen
Peripheral vasodilator	Ibudilast, Kallidinogenase, Limaprost, Nafronyl oxalate, Nicergoline
Streptokinase/streptodornase	
Others	
Herbal medications	Angelica extract, Artemisia asiatica extract, Avocado-soya titrated extract, Cimicifugae rhizoma extract, Clematidis Radix/Trichosanthes root/ Prunella spike extract, Coptis rhizome extract, Ginkgo biloba leaf extract, Hedera helicis folia extract, Hypericum extract, Milk-thistle extract, Motilitone, Pelargonium sidoides extract, Petasites hybridus folium extract, Phellinus linteus extract, Vaccinium myrtillus extract, Vitis vinifera extract, Zea mays L. titrated extract
Hormone-related agents	Anastrozole, Letrozole, Raloxifene, Tibolone
Metformin	

PIMs were evaluated based on the 2015 Beers criteria.[19] Among the PIMs, those associated with a high risk of delirium or a high risk of falls were included in the analysis. Levosulpiride (a prokinetic agent available in Korea) was also included; although it is not listed in the Beers criteria, it is known to frequently cause drug-induced movement disorders[20] and safer alternatives are available (Table 1).[21]

The high delirium-risk medications, which may induce adverse events such as delirium, confusion, or hallucination, included anticholinergics, antipsychotics, benzodiazepines, chlorpromazine, corticosteroids, H2-receptor antagonists, and sedative hypnotics (Table 1).[19] Anticonvulsants, antipsychotics, benzodiazepines, nonbenzodiazepines (benzodiazepine receptor agonist hypnotics), tricyclic antidepressants, selective serotonin reuptake inhibitors, and opioids were classified as high fall-risk medications (Table 1).[19]

The number of medications was calculated based on the number of active ingredients. Multi-component digestives, antacids, multivitamins, or herbal extracts were considered a single ingredient because they possess a single efficacy. Topical drugs and eye drops were not included because they are uncommonly associated with systemic adverse events. Polypharmacy and excessive polypharmacy was defined as regularly taking five or more medications and ten or more medications, respectively.[22–24] Post-operative delirium was diagnosed by psychiatric consultation using DSM-V criteria.[25]

2.3. Outcome measures

The primary outcome was intraoperative transfusion requirement.

2.4. Statistical analyses

The chi-square test was used to compare categorical variables. Multivariate logistic regression analysis was used to identify independent risk factors for intraoperative

Table 2 Factors associated with intraoperative transfusion.

Characteristics	No. (%)	Intraoperative transfusion, No. (%)		*p*
		Yes (n = 32)	No (n = 443)	
Sex				0.577
Male	215 (45.3)	16 (50.0)	199 (44.9)	
Female	260 (54.7)	16 (50.0)	244 (55.1)	
Age, years				0.253
<75	194 (40.8)	10 (31.3)	184 (41.5)	
≥75	281 (59.2)	22 (68.8)	259 (58.5)	
BMI, kg/m^2				<0.001
<18.5	26 (5.7)	6 (20.7)	20 (4.7)	
≥18.5	429 (94.3)	23 (79.3)	406 (95.3)	
CVD[a]				0.965
Yes	343 (72.2)	23 (71.9)	320 (72.2)	
No	132 (27.8)	9 (28.1)	123 (27.8)	
Diabetes				0.284
Yes	125 (26.3)	11 (34.4)	114 (25.7)	
No	350 (73.7)	21 (65.6)	329 (74.3)	
Dementia				0.259
Yes	17 (3.6)	0 (0)	17 (3.8)	
No	458 (96.4)	32 (100)	426 (96.2)	
CrCl[b]				0.654
≥30 mL/min	413 (90.8)	27 (93.1)	386 (90.6)	
<30 mL/min	42 (9.2)	2 (6.9)	40 (9.4)	
Surgical site				<0.001
Upper GI[c]	62 (13.1)	4 (12.5)	58 (13.1)	
Lower GI[d]	200 (42.1)	8 (25.0)	192 (43.3)	
HPB[e]	91 (19.2)	16 (50.0)	75 (16.9)	
Others[f]	122 (25.7)	4 (12.5)	118 (26.6)	
Tumor stage[g]				0.938
Stage 0−3	412 (93.4)	30 (93.8)	382 (93.4)	
Stage 4	29 (6.6)	2 (6.3)	27 (6.6)	
Delirium Risk Score[h]				0.981
0-1	454 (96.8)	31 (96.9)	423 (96.8)	
≥2	15 (3.2)	1 (3.1)	14 (3.2)	
Polypharmacy				0.761
Yes	240 (50.5)	17 (53.1)	223 (50.3)	
No	235 (49.5)	15 (46.9)	220 (49.7)	
DIM				0.571
Yes	200 (42.1)	15 (46.9)	185 (41.8)	
No	275 (57.9)	17 (53.1)	258 (58.2)	
FIM				0.859
Yes	365 (76.8)	25 (78.1)	340 (76.7)	
No	110 (23.2)	7 (21.9)	103 (23.3)	
Short-acting anticoagulant				0.589
Yes	4 (0.8)	0 (0)	4 (0.9)	
No	471 (99.2)	32 (100)	439 (99.1)	
Long-acting anticoagulant				0.009
Yes	6 (1.3)	2 (6.3)	4 (0.9)	
No	469 (98.7)	30 (93.8)	439 (99.1)	
Short-acting antiplatelet				0.838
Yes	18 (3.8)	1 (3.1)	17 (3.8)	
No	357 (96.2)	31 (96.9)	426 (96.2)	
Long-acting antiplatelet				0.503
Yes	128 (26.9)	7 (21.9)	121 (27.3)	
No	347 (73.1)	25 (78.1)	322 (72.7)	
Short-acting NSAID				0.886
Yes	17 (3.6)	1 (3.1)	16 (3.6)	
No	458 (96.4)	31 (96.9)	427 (96.4)	

Table 2 (*continued*)

Characteristics	No. (%)	Intraoperative transfusion, No. (%)		*p*
		Yes (n = 32)	No (n = 443)	
Long-acting NSAID				0.552
Yes	20 (4.2)	2 (6.3)	18 (4.1)	
No	455 (95.8)	30 (93.8)	425 (95.9)	
Peripheral vasodilator				0.701
Yes	23 (4.8)	2 (6.3)	21 (4.7)	
No	452 (95.2)	30 (93.8)	422 (95.3)	
Streptokinase/Streptodornase				0.038
Yes	8 (1.7)	2 (6.3)	6 (1.4)	
No	467 (98.3)	30 (93.8)	437 (98.6)	
Herbal medicine				0.818
Yes	82 (17.2)	6 (18.8)	76 (17.2)	
No	393 (82.7)	26 (81.3)	367 (82.8)	
Hormone-related agents				0.329
Yes	6 (1.3)	1 (3.1)	5 (1.1)	
No	469 (98.7)	31 (96.9)	438 (98.9)	
Metformin				0.640
Yes	89 (18.7)	5 (15.6)	84 (19.0)	
No	386 (81.3)	27 (84.4)	359 (81.0)	

BMI: body mass index, CVD: cardiovascular disease, CrCl: creatinine clearance, DIM: delirium-inducing medication, FIM: fall-inducing medication.

[a] CVD included hypertension, ischemic heart disease (unstable angina, stable angina, myocardial infarction), dyslipidemia, heart failure, atrial fibrillation, and cerebral infarction.

[b] There were 20 missing data entries for weight and CrCl.

[c] Upper gastrointestinal (GI): esophagus, stomach, and duodenum.

[d] Lower GI: intestine, colon, rectum, cecum, and anus.

[e] Hepato-pancreato-biliary (HPB) tumor: liver, pancreas, or gallbladder.

[f] Others included 93 breast cancer, 15 gynecologic cancer, 5 genitourinary cancer, and 9 other cancer types.

[g] There were 34 missing data entries for tumor stage.

[h] There were 6 missing data entries for delirium risk score.

transfusion. Factors having a *p*-value less than 0.05 from the univariate analysis, along with strong confounders of age and sex, were included in the multivariate analysis. Variables with a *p*-value less than 0.05 were entered by stepwise selection. They were removed if the *p*-value was greater than 0.1. Odds ratio (OR) and adjusted odds ratio (AOR) were calculated from the univariate and multivariate analyses, respectively. A *p*-value less than 0.05 was considered statistically significant. Attributable risk (%) was calculated as $(1-1/\text{AOR}) \times 100$. All statistical analyses were carried out using the Statistical Package for Social Sciences version 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 475 cancer patients who underwent preoperative CGA and cancer surgery were included in the analysis. Of 527 eligible patients who were scheduled for cancer surgery and who underwent CGA from January 2014 to June 2015, 54 patients were excluded due to refusal of surgery (n = 35), changed treatment plan (n = 13), and age less than 65 years (n = 4).

The median age of the included patients was 76 years (range, 65–96 years) and 281 patients (59.2%) were 75 years old or older. There were 215 male patients (45.3%). The patients' mean (SD) BMI was 23.8 (3.54) kg/m^2 (range, 15.0–40.4 kg/m^2). Thirty-two patients (6.7%) were transfused during surgery. BMI ($p < 0.001$), surgical site ($p < 0.001$), long-acting anticoagulants ($p < 0.01$), and streptokinase/streptodornase ($p < 0.05$) were significantly associated with transfusion (Table 2).

The number (percentage) of patients who were taking antithrombotics was 166 (34.9%); 10 (2.1%) were taking anticoagulants, 138 (29.1%) were taking antiplatelet medications, and three (2.2%) patients took both. As shown in Tables 2 and 3, patients taking long-acting anticoagulants before surgery showed an almost seven-fold higher intraoperative transfusion rate than those not taking long-acting anticoagulants before surgery. In contrast, patients who were taking long-acting antiplatelet medications before surgery did not show a significant propensity for transfusion.

Multivariate analysis showed that patients with BMI less than 18.5 kg/m^2 and those who underwent HPB surgery had an approximately 5-fold higher intraoperative transfusion rate compared to those with BMI $\geq$ 18.5 kg/m^2 and who underwent lower GI surgery, respectively (Table 3), with an attributable risk of approximately 80%. Long-acting anticoagulant use was the most significant factor for transfusion, with an AOR of 15.9 and attributable risk of almost 93.7%. Streptokinase/streptodornase therapy before surgery showed a marginally significant association with

Table 3 Univariate and multivariate regression analyses to identify predictors for intraoperative transfusion.

Characteristics	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Attributable Risk (%)
Female	0.82 (0.40–1.67)	0.91 (0.38–2.17)	
Age ≥ 75 years	1.56 (0.72–3.38)	2.20 (0.87–5.57)	
BMI < 18.5 kg/m^2	5.30 (1.94–14.46)**	5.25 (1.78–15.44)**	80.9
Surgical Site			
Upper GI[a]	1.66 (0.48–5.69)	0.91 (0.18–4.59)	
Lower GI[b]	1 (ref)	1 (ref)	
HPB[c]	5.12 (2.10–12.46)***	4.86 (1.89–12.48)**	79.4
Others[d]	0.81 (0.24–2.76)	0.98 (0.25–3.81)	
Long-acting anticoagulant	7.32 (1.29–41.57)*	15.93 (1.86–136.22)*	93.7
Streptokinase/Streptodornase	4.86 (0.94–25.09)	5.99 (0.95–37.88)	

Variables with a p value less than 0.05 (see Table 2) in addition to sex and age were included. OR: odds ratio.
Attributable risk was calculated as (1-1/Adjusted OR) × 100%.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] Upper gastrointestinal (GI): esophagus, stomach, and duodenum.
[b] Lower GI: intestine, colon, rectum, cecum, and anus.
[c] Hepato-pancreato-biliary (HPB) tumor: liver, pancreas, and gallbladder.
[d] Others included 93 breast cancer, 15 gynecologic cancer, 5 genitourinary cancer, and 9 other cancer types.

transfusion ($p = 0.054$). The AOR of transfusion in patients with streptokinase/streptodornase administration before surgery was 6.0 compared to those not receiving this medication. The area under receiver operating characteristic curve (AUROC) value for intraoperative transfusion was 0.779 (95% CI 0.687–0.872, $p < 0.001$) (Fig. 1).

4. Discussion

The main finding of this study was that long-acting anticoagulants (AOR 15.9, 95% CI 1.9–136.2), BMI less than 18.5 kg/m^2 (AOR 5.3, 95% CI 1.8–15.4), and HPB surgery (AOR 4.9, CI: 1.9–12.5) were significantly associated with intraoperative transfusion after adjusting for confounders. The attributable risks of long-acting anticoagulants, BMI, and HPB surgery were 93.7, 80.9, and 79.4%, respectively.

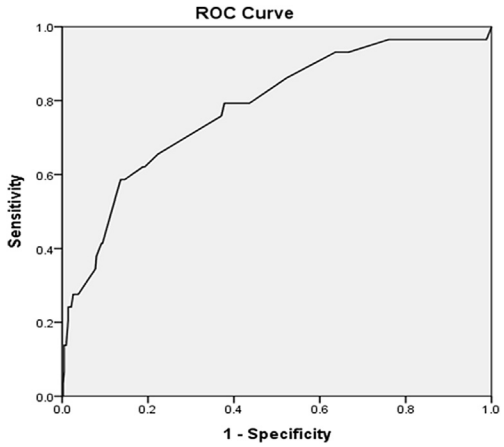

Figure 1 Area under receiver operating characteristic curve for intraoperative transfusion. AUROC is 0.779 (95% CI 0.687–0.872, p < 0.001).

CGA was originally developed by geriatricians as a multidomain evaluation for older patients. CGA comprises functional status, comorbidity, polypharmacy, cognition, psychological status, social support, and nutritional status. It has been reported that CGA is a fundamental aid for evaluation and treatment planning of older cancer patients. Ample evidence supports the value of CGA for predicting overall morbidity and mortality in geriatric cancer patients.[26–28] It has become a predictor for intra- and postoperative complications, medical treatment, cognition, geriatric syndromes, and extrinsic frailty in elderly cancer patients.[29–33]

Unlike long-acting anticoagulants, which showed significant effects on intraoperative transfusion, antiplatelet drugs did not affect blood transfusion, regardless of their half-lives or duration of action. The CGA was performed within 7 days prior to surgery; therefore, we assumed that patients included in the medication-intake group received the antithrombotics during the 7 days preceding surgery. According to a previous study, patients who stopped taking aspirin 3–7 days preoperatively had little or no increased requirement for blood transfusion.[34,35] Although the surgical bleeding risks associated with clopidogrel, another antiplatelet drug, have not been completely characterized, some experts suggest that this medication has a safety profile similar to that of aspirin in this setting.[36] In contrast, bleeding complications have been shown to be increased in patients taking warfarin. Currently, it is recommended to discontinue warfarin 5 days before surgery, as it takes 5 days for the INR to normalize after stopping warfarin.[37]

We found that blood transfusion was clearly associated with low BMI. Similar results of other studies suggest that low BMI is a common risk factor for intraoperative transfusion.[38,39] Low BMI has been associated with an increased risk of excessive blood loss. Especially in heart surgery, low BMI has been shown to be a risk for reoperation because of excessive bleeding.[40] However, for hip and knee arthroplasty, BMI was not found to be associated with blood loss in either hip- or knee-replacement patients.[41,42] The

discrepancy is attributable to the different surgery types. It is not surprising that a low BMI was associated with intraoperative blood transfusion in our study, because many patients with cancer experience significant weight loss before surgery due to poor oral intake and malnourishment.

HPB cancer was found to be associated with transfusion in our study. Other studies have reported that HPB surgery is among the most common factors associated with transfusion.[43,44] The liver is a highly vascular organ, and substantial blood loss is common during liver surgery.[45–47] Therefore, patients undergoing liver resection may be at increased risk for excessive blood loss and a subsequent need for blood transfusion.

The study is limited by its retrospective, single-center design. Nevertheless, this study demonstrates the value of a CGA team-directed comprehensive medication assessment using the most current evidence-based screening tools to detect medication-related risk factors of intraoperative transfusion. Especially, it was recommended that long-acting anticoagulants be withdrawn at least seven days before surgery.

5. Conclusion

The results of this study show that medication use in geriatric cancer patients has an impact on transfusion during surgery; in particular, the preoperative use of long-acting anticoagulants is associated with an increased risk of intraoperative transfusion. This finding also demonstrates the value of medication screening, as a component of a multidisciplinary comprehensive geriatric assessment, for reducing the risks of medication-related complications in the perioperative period.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

The authors declare that they have no competing interests.

Authors' contributions

YMJ, JEC, KK, and HSG made substantial contributions to conception and design of study. YMJ, KSC, MSJ, EL, and BKL, made acquisition and analysis of data. YMJ, JEC, and JY made an interpretation of data. JEC and HSG have been involved in drafting and revising the manuscript. All authors approved final version of manuscript.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2019.06.005.

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