

Is Blood Loss Greater in Elderly Patients under Antiplatelet or Anticoagulant Medication for Cervical Spine Injury Surgery? A Japanese Multicenter Survey

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Abstract:

Introduction: In elderly patients with cervical spinal cord injury, comorbidities such as cardiovascular and cerebrovascular diseases are common, with frequent administration of antiplatelet/anticoagulant (APAC) drugs. Such patients may bleed easily or unexpectedly during surgery despite prior withdrawal of APAC medication. Few reports have examined the precise relationship between intraoperative blood loss and history of APAC use regarding surgery for cervical spine injury in the elderly. The present multicenter database survey aimed to answer the question of whether the use of APAC drugs affected the amount of intraoperative blood loss in elderly patients with cervical spinal cord trauma.

Methods: The case histories of 1512 patients with cervical spine injury at 33 institutes were retrospectively reviewed. After excluding cases without spinal surgery or known blood loss volume, 797 patients were enrolled. Blood volume loss was the outcome of interest. We calculated propensity scores using the inverse probability of treatment weighting (IPTW) method. As an alternative sensitivity analysis, linear mixed model analyses were conducted as well.

Results: Of the 776 patients (mean age: 75.1±6.4 years) eligible for IPTW calculation, 157 (20.2%) were taking APAC medications before the injury. After weighting, mean estimated blood loss was 204 mL for non-APAC patients and 215 mL for APAC patients. APAC use in elderly patients was not significantly associated with surgical blood loss according to the IPTW method with propensity scoring or linear mixed model analyses. Thus, it appeared possible to perform surgery expecting comparable blood loss in APAC and non-APAC cases.

Conclusions: This multicenter study revealed no significant increase in surgical blood loss in elderly patients with cervical trauma taking APAC drugs. Surgeons may be able to prioritize patient background, complications, and preexisting conditions over APAC use before injury when examining the surgical indications for cervical spine trauma in the elderly.

Keywords:

cervical spine injury, elderly patients, blood loss volume, comorbidity, antiplatelet/anticoagulant drugs

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Introduction

The aging population is a global phenomenon that has affected the epidemiology of traumatic spinal cord injury, with the frequency of elderly patients with cervical spinal cord trauma on the rise¹⁻⁵. The physiological changes associated with aging are thought to be the primary cause of increased susceptibility to acute injury, delayed recovery, and persistent debilitation⁶. Managing cervical spine injuries in the elderly is often complicated by the presence of multiple medical complications, including decreased cardiopulmonary function and poor bone quality⁷. Furthermore, in elderly patients with cervical spinal cord trauma, such comorbidities as cardiovascular and cerebrovascular diseases are common, requiring the use of antiplatelet/anticoagulant (APAC) drugs. Those patients may bleed unexpectedly during surgery despite the prior withdrawal of APAC medication. However, few reports have examined the precise relationship between intraoperative blood loss and a history of APAC use regarding surgery for cervical spine trauma in the elderly.

The present multicenter database review aimed to answer the question of whether the use of APAC drugs impacted intraoperative blood loss in elderly patients with cervical spine injury.

Materials and Methods

This investigation was conducted as a multicenter joint study of the Japan Association of Spine Surgeons with Am-

bition. The protocol of this study was approved by our Institutional Review Board (No. 4824) and all other participating institutions' review boards.

Cohort construction

We retrospectively reviewed the case histories of 1512 patients with cervical spine injury in the period from 2010 to 2020 among 33 institutes throughout Japan. Patients who did not receive surgery or whose blood loss status was unknown were excluded, resulting in 797 patients for analysis. Informed consent was obtained in the form of an optout system at each institute. Patients declining participation were excluded. The study design was approved by the ethics review board for clinical research at each institute and was in compliance with the Helsinki Declaration. The flowchart of the patients included in the study is shown in Fig. 1.

Evaluations

Survey items included blood loss, use of APAC medication, age, sex, blood test data, preinjury activities of daily living (ADLs), previous medical conditions, medications used, complications other than cervical spine injury, trauma characteristics (presence of fracture, presence of dislocation, and location of fracture), American Spinal Cord Injury Association (ASIA) classification, and facility at which the case was collected. Blood volume loss was the primary outcome. In the case of two-stage surgery, the total volume was used. If the amount of blood loss was described as small without any numerical value, it was treated as 10 mL. The difference

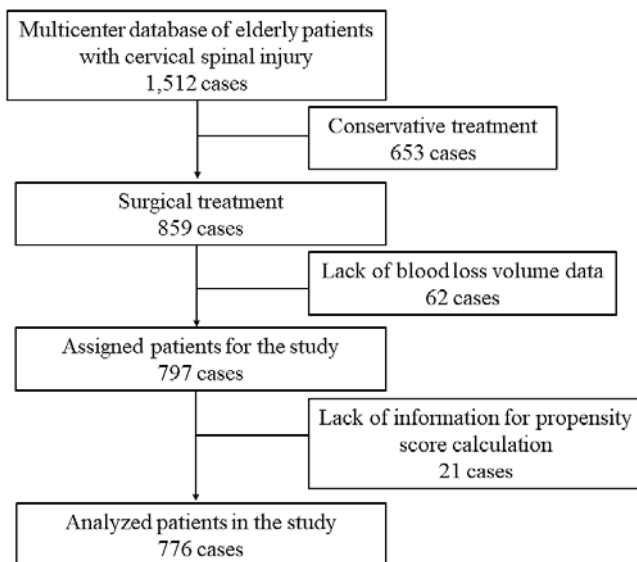


Figure 1. Patient flowchart.

in bleeding volume between the group with (APAC+) and without (APAC-) APAC use was examined.

Statistical analysis

Since the background factors of the APAC+/- groups were different, we calculated propensity scores weighted by their inverse by means of the inverse probability of treatment weighting (IPTW) method. The candidate factors included in propensity scores were those able to be extracted from the database: age, sex, total protein, albumin, hemoglobin, preinjury ADLs, and presence or absence of medical history (cerebrovascular disease, cognitive impairment, Parkinson's disease, diabetes mellitus, rheumatoid arthritis, osteoporosis, hypertension, cardiac disease, respiratory disease, renal disease, history of surgery for musculoskeletal disease, or other). Preinjury medications (number of medications, antipsychotics, anxiolytics, sleeping pills, vitamin D, bisphosphonates, other osteoporosis drugs, nonprotein extract from inflamed rabbit skin inoculated with the vaccinia virus, nonsteroidal antiinflammatory drugs [NSAIDs], pregabalin/milogabalin, serotonin-norepinephrine reuptake inhibitors, tramadol, other analgesics, antihypertensive drugs, antiarrhythmic drugs, steroids, diabetes drugs, or other drugs), presence of concomitant trauma (head, chest, abdomen, upper extremity, lower extremity, pelvis, thoracolumbar spine, or other), type of cervical spine injury (presence of fracture, presence of dislocation, and level of fractured vertebra), presence of ankylosis (ossification of the posterior longitudinal ligament, ossification of the ligamentum flavum [OLF], diffuse idiopathic skeletal hyperostosis, or other cervical ankylosis), number of days elapsed since injury at the time of surgery, surgical method (posterior decompression, posterior decompression and fusion, anterior fusion, anterior decompression and fusion, posterior-anterior combined, or anterior-posterior combined), ASIA score (sum of key muscle manual muscle testing: 0-100 points), and enrollment fa-

cility data were collected as well. Logistic regression analysis was performed with the above factors as explanatory variables and APAC+/- as a response variable, with the best model selected using a stepwise method based on the Akaike Information Criterion (AIC). Ultimately, cerebrovascular disease, cardiovascular disease, respiratory disease, number of medications, osteoporosis drugs, antihypertensive drugs, antiarrhythmic drugs, diabetes drugs, complication of lower extremity trauma, and OLF were selected for analysis. Twenty-one patients with missing items were excluded from propensity score calculations, resulting in a final number of 776 patients. The c-statistic, an indicator of appropriateness of propensity score, was high at 0.898. Weighted *t*-tests were used to evaluate differences in the amount of blood loss between APAC+ and APAC- patients.

To further explore the question of whether blood loss differed between the APAC+/- groups, we also conducted linear mixed model analyses as another form of sensitivity analysis. APAC+/- and surgical intervention factors were considered as fixed effects, whereas uncontrollable factors were considered as random effects in the explanatory variables. The fixed effects were APAC+/-, number of days elapsed since injury until the day of surgery, surgical method, and surgical time. Random effects included age (categorized by age group), sex, disease history, presence of concomitant injury, presence of cervical spine fracture and/or dislocation, presence of spinal ankylosis, presence of intraoperative complications, and registered institution. The response variable was the amount of blood loss. In addition to the crude analysis model with only APAC+/- as the fixed effect, adjusted analysis models in which fixed effects other than APAC+/- were included as adjusting factors were also calculated. Other fixed effects were candidate factors that passed variable selection by stepwise model testing based on AIC. Random effects were included in both the crude and adjusted analysis models.

All statistical analyses were carried out using the statistical package R, version 4.1.0 (available at: <http://www.r-project.org>). The level of significance was set at $p < 0.05$.

Results

A total of 859 patients underwent surgery for cervical spine injury. Forty-five patients with unknown blood loss status were excluded. Twenty-one patients with missing items were dropped from propensity score calculations with the IPTW method. Of the remaining 776 patients (534 [68.8%] male and 242 [31.2%] female), 157 (20.2%) were taking APAC medications before the injury. The characteristics of patients with and without APAC agents are summarized in Table 1. APAC+ patients were significantly older and more predominantly male. No significant differences were seen for preoperative ASIA motor score, days after injury, frequency of surgery within 1 day of injury, number of fused vertebrae, operative time, or blood loss.

The IPTW method showed no statistically significant dif-

Table 1. Characteristics of the Study Population.

	APAC- (n=619)	APAC+ (n=157)	p-value
Age (years)	74.7±6.4	76.3±6.1	<0.01
Sex (male:female)	411:208	123:34	<0.01
Comorbidities [patients (%)]	484 (78.2)	155 (98.7)	<0.001
Preoperative ASIA motor score	71±34	73±33	0.46
Days between injury and operation	22±57	32±114	0.30
Frequency of surgery within 1 day of injury [patients (%)]	111 (17.9)	19 (12.1)	0.09
Fused vertebrae	2.3±2.2	2.4±2.2	0.83
Surgical time (min)	167±76	164±72	0.62
Blood loss volume (mL)	214±359	206±315	0.80

Notes: Values are expressed as mean±standard deviation or patient number (%). The p-values of differences between the APAC+and – groups were calculated by Welch’s *t*-test or Fisher’s exact test.

Abbreviations: APAC, antiplatelet/anticoagulant; ASIA, American Spinal Cord Injury Association

Table 2. Estimates of Blood Loss and Difference between Patients with and without APAC Use by the IPTW Method.

	Blood loss (mL)			p-value
	APAC-	APAC+	Difference	
Crude	214 (185–242)	206 (157 to 256)	-7 (-50 to 64)	0.80
Weighted	204 (176 to 231)	215 (81 to 348)	11 (-125 to 148)	0.87

Notes: Values are expressed as estimated mean (95% confidence interval). Crude values were estimated by unweighted *t*-tests. Weighted values were estimated by IPTW *t*-tests.

Abbreviations: APAC, antiplatelet/anticoagulant; IPTW, inverse probability of treatment weighting

ferences in blood loss for surgeries on APAC users and non-APAC users. After weighting, mean estimated blood loss was 204 mL for APAC- and 215 mL for APAC+ (Table 2). Comparing the amount of blood loss in patients who received surgery within 1 day of injury, intraoperative blood loss was 250±315 mL for APAC- and 334±318 mL for APAC+ (p=0.3).

As a subanalysis, we compared patients taking any antiplatelet drug (AP+) (n=78) and APAC- patients (n=619) as well as patients receiving any anticoagulant drug (AC+) (n=55) and APAC- patients. The propensity scores used for the IPTW method were calculated from the same items as for APAC as a whole, providing c-statistic scores of 0.907 for AP+ vs. APAC- and 0.879 for AC+ vs. APAC-, which fully met the condition of assessing the assumption of strongly ignorable treatment assignment. The estimated blood loss for AP+ and AC+ was 164 and 195 mL, respectively, and neither unweighted nor weighted analyses were significantly different from APAC- values (Table 3). There was also no significant difference in blood loss between the 78 AP-only patients and the 55-AC only patients (p=0.76, IPTW *t*-test, c-statistic score: 0.720).

In a further sensitivity analysis, similar results were obtained by estimating the effect on blood loss using mixed models, with no significant relationship between APAC use and surgical blood loss (Table 4). Comparable results were

also obtained in adjusted models. Whereas surgical method and surgical time were significantly associated with surgical blood loss, APAC+/- status was not.

Fisher’s exact test was adopted to examine the relationship between intraoperative complications and the presence or absence of APAC medication. Twenty cases (3.2%) of complications were recorded in the APAC- group, which included dural tear (10 cases), cerebral infarction (4 cases), difficulty controlling hemostasis of the epidural venous plexus (2 cases), cardiac arrest due to massive bleeding (1 case), lamina fracture (1 case), screw perforation of lamina (1 case), and screw perforation of the transverse foramen (1 case). Complications were encountered in 7 cases (4.5%) in the APAC+ group, namely, dural tear (3 cases), lamina fracture (1 case), difficulty in extubation due to airway edema (1 case), spinal cord injury (1 case), and radial nerve palsy (1 case). There was no significant difference in the incidence of intraoperative complications between the groups (p=0.46). Massive bleeding of more than 1000 mL was noted in 14 cases (2.3%) in the APAC- group and 5 cases (3.2%) in the APAC+ group, the incidence of which was comparable (p=0.56).

Discussion

The present investigation evaluated whether the use of

Table 3. Estimates of Blood Loss and Difference between Patients with and without AP or AC Use by the IPTW Method.

	Blood loss (mL)			p-value
	Medication-	Medication+	Difference	
AP				
Crude	214 (185 to 242)	210 (147 to 273)	-4 (-65 to 72)	0.91
Weighted	204 (176 to 232)	164 (79 to 248)	-41 (-129 to 48)	0.36
AC				
Crude	214 (185 to 242)	194 (89 to 298)	-20 (-88 to 128)	0.71
Weighted	212 (185 to 239)	195 (36 to 353)	-17 (-178 to 144)	0.83

Notes: Values are expressed as estimated mean (95% confidence interval). Crude values were estimated by unweighted *t*-tests. Weighted values were estimated by IPTW *t*-tests. Abbreviations: AP, antiplatelet; AC, anticoagulant; IPTW, inverse probability of treatment weighting

Table 4. Estimates of Mixed Model Effects on Blood Loss Volume.

	Crude effect (mL)	p-value	Adjusted effect (mL)	p-value
APAC (+)	-14±28	0.61	-14±26	0.59
Days after injury (+1 day)			0.0±0.1	0.75
Surgical method				
(compared with posterior fusion)				
Posterior decompression			-79±32	0.02
Posterior decompression and fusion			-35±29	0.22
Anterior fusion			-98±53	0.06
Anterior decompression and fusion			-10±76	0.89
Posterior-anterior combined			-21±75	0.78
Anterior-posterior combined			-272±130	0.03
Surgical time (+10 min)			16±2	<0.001

Notes: Effects are presented as estimated mean±standard error. The fixed effect of the crude model consists only of APAC. The fixed effect of the adjusted model consists of APAC and other candidate factors selected by the stepwise method. Both the crude and adjusted models were adjusted by random effects. Abbreviation: APAC, antiplatelet/anticoagulant

APAC drugs affected the amount of intraoperative blood loss using a multicenter database of elderly patients with cervical spinal cord injury. Both the IPTW method with propensity scores and mixed models revealed no significant difference in the amount of bleeding in patients with and without APAC medication before the injury. Our findings indicate that comparable blood loss and rates of complications and massive bleeding may be expected in elderly cervical trauma cases regardless of APAC use.

As the rate of elderly people increases, interest is mounting on cervical trauma and care in this group. Regardless of the mechanism, one form of trauma that is rising in the elderly is cervical spine fracture⁸. Currently, older adults aged 65 years and older account for 25% of all trauma hospitalizations involving this injury, and cervical spine fractures account for 43% of all traumatic vertebral fractures^{8,9}.

In recent years, there has been an increase in the number of spine surgeries performed on elderly patients, with the percentage of patients with cerebral and cardiovascular diseases also rising¹⁻⁵. Such patients are more frequently using APAC drugs to prevent recurrent cerebral and cardiovascular

events. In the present study of elderly cases, as many as 20.2% of patients were taking APAC agents before the injury. For scheduled surgeries, these drugs can be withdrawn to avoid the risk of increased intraoperative bleeding. However, it is often necessary to intervene without a sufficient withdrawal period for cervical spine trauma and other emergency cases.

Several studies have examined the impact of APAC drugs on perioperative blood loss, operative time, perioperative complications, and clinical outcome in diseases other than cervical spine injury. In a meta-analysis of 474 cases, continued aspirin administration caused a 1.5-fold increase in perioperative blood loss, with little effect on complications or surgical outcome. In addition, aspirin use led to a 7.2-fold increase in reoperation rate for tonsil surgery, a 2.7% transfusion rate in transurethral prostate resection, and death in intracranial surgery¹⁰.

Reports on spine surgery have suggested preoperative aspirin medication as a risk factor for postoperative epidural hematoma^{11,12}. Soleman et al. observed that the amount of blood loss during posterior lumbar decompression under

continuous aspirin was 1.5 times that of a discontinuation group, with no cases of massive blood loss requiring transfusion¹³). Park et al. witnessed no significant difference in perioperative blood loss in lumbar fusion of two or more intervertebral levels according to the presence or absence of aspirin intake among patients who did not use other NSAIDs. In patients receiving other NSAIDs, perioperative bleeding was significantly higher in the withdrawal and continuation groups than in the aspirin-free group¹⁴). To the best of our knowledge, no studies have addressed the effects of APAC drugs on cervical spine injury surgery in the elderly. We found no significant difference in the amount of bleeding according to the presence or absence of APAC medication for both the IPTW method with propensity scores and linear mixed model analyses, with bleeding volume in both groups approximately 200 mL. Moreover, no significant differences in intraoperative complications or massive bleeding events were seen between the groups. Subanalyses on AP and AC also displayed no significant changes; estimated blood loss volume was 164 and 195 mL, respectively.

One of the strengths of the current study was the large number of surgical cases for cervical spine injuries due to its multicenter design. However, this investigation also had several limitations. First, it was a retrospective case series with no control group. The population may have also been heterogeneous from bias of the participating medical institutions, which were mainly tertiary care facilities. In addition, the background and general health of the patients were inevitably considered when deciding on treatment. Although we were unable to accurately investigate the presence or absence of APAC withdrawal, there were no significant differences in the number of days from injury to surgery or the frequency of surgery within 1 day of injury between cases with and without APAC medication. Furthermore, in patients undergoing surgery within 1 day of injury, the amount of blood loss did not differ significantly between the groups. Another limitation of this study was the lack of follow-up data; APAC-related bleeding complications may have occurred outside of the observation period. Lastly, the time between injury and surgery was relatively long in this study. Although we could not obtain precise data on whether medication such as warfarin was withdrawn or switched, a waiting period before surgery may be desirable depending on the surgical invasion and general patient condition. This study demonstrated that even in patients using APAC drugs, intraoperative and perioperative countermeasures, including the withdrawal of medication as much as possible, might be taken to ensure safe surgery without increasing blood loss.

Conclusion

This study addressed the question of whether the use of APAC drugs impacted the amount of bleeding in surgery for elderly patients with cervical spinal cord trauma using a multicenter database. Since APAC use was not significantly associated with blood loss after multiple testing, surgeons

may be able to prioritize patient background, complications, and preexisting conditions over APAC use before injury when examining the surgical indications for cervical spine trauma in the elderly. Further studies are needed to validate our findings.

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Informed Consent: Informed consent for publication was obtained from all participants in this study.

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