Original Article

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Acute Ischemic Stroke after Non-Cardiac, Non-Neurologic and Non-Major Vascular Surgery During Index Hospitalization: A Retrospective Matched Case-Control Study

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Objective: Incidence and risk factors for acute ischemic stroke (AIS) during index hospitalization period following non-major surgery were not well characterized.

Methods: This retrospective, matched case-control study was conducted by reviewing the medical records (from January 2019 to December 2022) in three general hospitals located in Kaohsiung City, Taiwan. Patients who presented with newly onset neurologic deficits after non-cardiac, non-neurologic, and non-major vascular surgery during the index hospital stay period were evaluated with brain imaging studies to confirm the development of AIS. The potential risk factors for perioperative AIS were compared with the randomly selected matched controls in a ratio of 1:5 from the same database.

Results: A total of 103,348 patients were included in the 4-year study period and AIS was radiographically confirmed in 12 patients. Two AIS patients expired during the hospital stay period and all remaining AIS patients still experienced moderate-to-severe functional disability at hospital discharge. Multivariate logistic regression analysis illustrated that patients who received regular antiplatelet therapy (adjusted odds ratio [AOR] 5.22, 95% confidence interval [CI] 1.03 – 26.44; $p = 0.046$) and those who received intraoperative red blood cell (RBC) transfusions (AOR 52.21, 95% CI 4.15 – 656.46; $p = 0.002$) were the two most significant independent variables for perioperative AIS.

Conclusions: Our study finds that incidence of perioperative AIS after non-cardiac, non-neurologic, and non-major vascular surgery was 0.01% with a high in-hospital mortality rate of 16.7%. Survivors suffered moderate-to-severe functional impairment. Patients taking regular antiplatelet therapy and those who required RBC transfusions intra-operatively, particularly during spinal surgery, were associated with higher risks of perioperative AIS.

Key words: stroke, acute ischemic stroke, perioperative stroke, risk of perioperative stroke, non-cardiac surgery

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Introduction

Perioperative acute ischemic stroke (AIS) is a serious postoperative complication that can lead to increased mortality and morbidity after surgery, especially in major cardiovascular surgeries and neurosurgeries.[1] The development of AIS after non-cardiac, non-neurologic, and non-major vascular surgery is particularly concerning in clinical anesthesia, as this relatively rare perioperative complication is likely to result in medical legal issues. According to several large cohort studies, the overall incidence of perioperative AIS within 30 days of non-cardiac, non-neurologic, and non-vascular surgery ranges from 0.08% – 0.7%.[2-5] Perioperative AIS was associated with a 3 to 8-fold increase in 30-day all-cause mortality[3,4] and longer length of hospital stay.[4] Commonly reported risk factors associated with perioperative AIS in these low-risk surgical patients include old age (> 65 years), history of stroke, cardiac disease, renal dysfunction, and atrial fibrillation.[3-5] However, these large cohort studies did not include important variables such as detailed patient characteristics and anesthetic/surgical related factors in their analyses of AIS risk factors. We thus performed this retrospective, matched case-control study to more comprehensively analyze the risk factors associated with developing AIS after non-cardiac, non-neurologic, and non-major vascular surgery.

Materials and Methods

Patient database

This retrospective chart-review matched case-control study was carried out in three general hospitals located in Kaohsiung City of Taiwan. The study was approved by the Institutional Review Board of E-Da Hospital (approval number EMRP-110-057). Since all clinical data were collected from routine medical records, the need for written informed consent from patients was waived. This study included all patients who received anesthesia management for surgical interventions from January 1, 2019 to December 31, 2022 in E-Da Hospital, E-Da Cancer Hospital, and E-Da Dachang Hospital located at Kaohsiung City, Taiwan (Fig. 1). Patients who received cardiac surgery, major aortic surgery, carotid endarterectomy, or thrombectomy and craniotomy for traumatic brain injury or intracranial hemorrhage was excluded (Fig. 1).

Definition of perioperative acute ischemic stroke

All patients who presented with newly onset neurological deficits or unusual mental status changes after surgery during the index hospital stay period were evaluated by clinical neurologists. Computer tomography and/or magnetic resonance imaging of the brain were performed in those with acute neurological signs that suggested perioperative stroke. Only patients with stroke symptoms and comparable radiographical evidence of ischemic strokes were included in this study.

Matched control patients

Matched controls were surgical patients who underwent surgical interventions that required regional or general anesthesia during the same study period. These patients did not develop obvious neurological signs nor unusual mental status changes suggestive of an acute stroke from the post-operative period to before hospital discharge. Matched control patients were randomly selected from the same clinical database after matching with the calendar year of operation in a 1:5 ratio.

Statistical analysis

The values of numeric and categorical variables between two study groups were compared using an independent two-sample t test and chi-square test respectively. A condi-

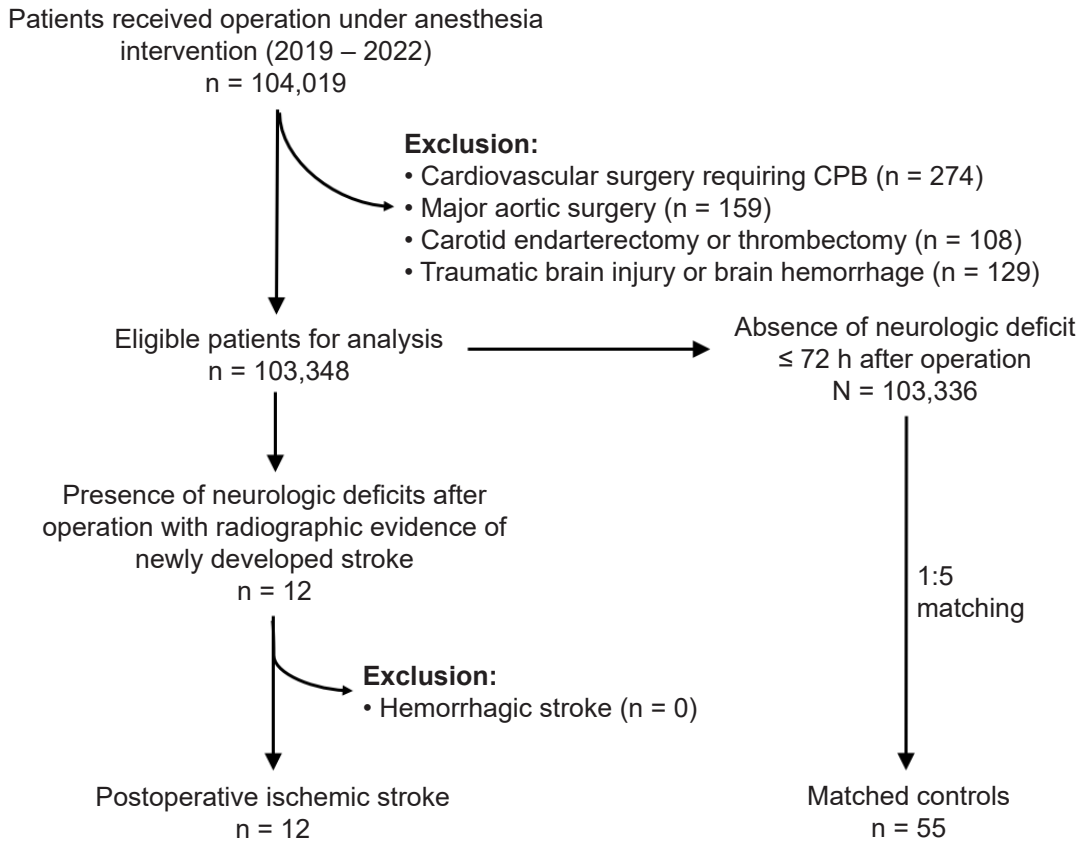

Fig. 1 Study flow chart.

tional logistic regression model was adopted to evaluate the association between these variables and the development of perioperative AIS. Statistical significance was accepted at a level of $p < 0.05$. All analyses were carried out using the SAS software, version 9.1 (SPSS software, version 24.0 [IBM, Armonk, NY]).

Results

Overall incidence and mortality rate of post-operative AIS

A total of 103,348 patients received non-cardiac, non-neurological, and non-major vascular surgeries during the 4-year study period in these three hospitals; and of these patients, 12 developed acute clinical signs suggestive of a cerebral accident after surgery (Fig. 1). Ischemic stroke was confirmed radiographically in all 12 patients and none of these patients were found to have an intracranial hemorrhage (Fig. 1 & Table 1). Therefore, the

Table 1. Patient characteristics of postoperative stroke vs. matched controls.

Characteristics	Stroke cases n = 12	Matched controls n = 55	*p* value
Age (years)	65.2 ± 10.2	52.0 ± 19.2	0.026
Gender (M)	6 (50)	31 (56)	0.688
BMI (kg/m^2)	24.5 ± 2.1	25.0 ± 5.1	0.759
ASA PS			0.159
I – II	5 (42%)	35 (66%)	
≥ III	7 (58%)	20 (34%)	
Major comorbidities			
Hypertension	8 (67)	21 (38)	-
Diabetes mellitus	5 (42)	15 (27)	-
Cardiovascular diseases	2 (17)	6 (11)	-
Atrial fibrillation	1 (8)	3 (5)	-
Previous stroke	2 (17)	3 (5)	-
Renal disease	5 (42)	9 (16)	-
Use of antiplatelet agents (y)	5 (42)	5 (9)	0.012

Data are presented as mean ± SD or n (%).
$p < 0.05$ is considered as statistically significant.
ASA PS: American Society of Anesthesiologists Physical Status; M: male; y: yes.

overall incidence of post-operative AIS during the index hospital stay period was 0.01% in our study. Two patients expired after developing AIS (16.7% mortality) and all stroke patients who survived to hospital discharge had moderate-to-severe disability (modified Rankin score ≥ 3) (Table 1). Among these 12 stroke patients, 5 patients received spinal surgery and 3 patients received exploratory laparotomies (Table 1).

Associations and correlations

Compared with the matched controls, patients who developed perioperative AIS were significantly older (52.0 ± 19.2 vs. 65.2 ± 10.2; $p = 0.026$) and a higher proportion were taking regular oral anti-platelet agents before surgery (9% vs. 42%; $p = 0.012$) (Table 2). There were no significant differences in gender, physical status, and common comorbidities between the two groups (Table 2).

Factors possibly linked to AIS development

Table 3 shows the surgical and anesthesia-related factors that may be associated with the development of AIS during the perioperative period. Significantly more patients that developed AIS underwent spinal surgery and were placed in the prone position during surgery (Table 3). Patients who developed post-operative AIS were also found to have higher average intra-operative estimated blood loss volumes and more episodes of intra-operative hemodynamic instability (Table 3). The types of surgical emergencies and anesthesia techniques were similar between the matched control and AIS groups (Table 3).

Multivariate logistic regression findings

Patient characteristics and surgery-related factors that were associated with perioperative AIS were further analyzed using multivariate

Table 2. Surgical and anesthesia factors of postoperative stroke vs matched controls.

Characteristics	Stroke cases n = 12	Matched controls n = 55	*p* value
Emergency operation (Y)	3 (25)	10 (18)	0.588
Types of operation			
Spinal surgery	5 (42)	5 (9)	0.012
Orthopedic surgery	1 (8)	12 (22)	NS
Major abdominal surgery	4 (33)	10 (18)	NS
Brain surgery	0	1 (2)	NS
Other surgeries	2 (17)	27 (49)	NS
Surgical positioning			
Supine	7 (59)	43 (78)	NS
Prone	4 (33)	4 (7)	0.029
Sitting	1 (8)	3 (5)	NS
Lateral decubitus	0	1 (2)	NS
Lithotomy	0	4 (7)	NS
Total operation time (hours)	4.2 ± 2.2	3.3 ± 2.3	0.156
Anesthesia technique			0.157
General	11 (92)	38 (69)	
Regional or IVS	1 (8)	17 (31)	
Estimated blood loss (mL)	374 ± 709	75 ± 136	0.006*
RBC transfusion (Y)	5 (42)	1 (2)	0.000
Episodes of significant ΔSBP#	8.7 ± 15.0	1.8 ± 3.9	0.004*
Use of vasoactive agents (Y)	5 (42)	12 (22)	0.164

Defines as changes from the baseline value and lasted for more than 5 minutes. Data are presented as mean ± SD or n (%). * $p < 0.05$ is considered as statistically significant.

IVS: intravenous sedation; RBC: red blood cells; ΔSBP: changes in systolic blood pressures; M: male; Y: yes.

Table 3. Surgical and anesthesia factors of postoperative stroke vs matched controls.

Patient ID	Gender	Age	ASA PS	Operation	Intraoperative positioning	Operation time (minutes)	Diagnosis of stroke	Outcome at hospital discharge
1	F	80	IV	Nephrectomy	Supine	570	Multifocal infarctions	STHD; mRS = 3
2	M	65	II	Lumbar spinal fusion	Prone	330	Carotid artery stenosis	STHD; mRS = 3
3	F	71	III	Ureterorenoscopy	Supine	120	Right MCA occlusion	STHD; mRS = 5
4	F	43	I	Acromioplasty	Sitting	120	Severe ICA stenosis	STHD; mRS = 4
5	M	70	I	Intraspinal tumor excision	Prone	390	Right MCA infarction	Death; mRS = 6
6	M	55	III	Lumbar spinal fusion	Prone	165	Right ICA & MCA thrombus	STHD; mRS = 4
7	M	63	III	Left below knee amputation	Supine	145	Multifocal infarctions	STHD; mRS = 4
8	F	82	III	Exploratory laparotomy	Supine	330	Carotid artery stenosis	STHD; mRS = 5
9	F	70	IIIE	Exploratory laparotomy	Supine	340	Multifocal infarctions	STHD; mRS = 4
10	M	62	IIE	Lumbar spinal fusion	Prone	165	Vertebral artery hypoplasia	STHD; mRS = 5
11	M	62	I	Cervical spinal discectomy	Supine	200	Right MCA infarction	Death; mRS = 6
12	F	59	IVE	Exploratory laparotomy	Supine	300	Multifocal infarctions	STHD; mRS = 4

ASA PS: American Society of Anesthesiologists Physical Status; E: emergency operation; ICA: internal carotid artery; MCA: middle cerebral artery; mRS: modified Rankin score; STHD: survival to hospital discharge.

logistic regression. After the analysis, it was found that there were no significant differences in age between the AIS patients and matched controls. However, current anti-platelet use remained an independent risk factor for developing peri-operative AIS (adjusted odds ratio [AOR] 5.22, 95% confidence interval [CI] 1.03 – 26.44; $p = 0.046$) (Table 4). Spinal surgery was associated with an increased risk of developing AIS, although the difference was not statistically significant ($p = 0.064$) (Table 4). Intra-operative red blood cell transfusions were associated with significantly higher risks of developing AIS (AOR 52.21, 95% CI 4.15 – 656.46; $p = 0.002$) (Table 4).

Table 4. Multivariate conditional logistic regression analysis.

Patient characteristic variables				
Risk factors	β	95% CI	Adjusted odd ratio	*p*
Age (years)	0.04	0.99 – 1.10	1.04	0.100
Gender (M : F)	0.28	0.33 – 5.31	1.33	0.690
ASA PC (≥ III)	0.05	0.23 – 4.82	1.05	0.951
Use of antiplatelet agents (y)	1.65	1.03 – 26.44	5.22	0.046*
Surgical-related variables				
Risk factors	β	95% CI	Adjusted odd ratio	*p*
Spine surgery	2.86	0.85 – 355.18	17.37	0.064
Prone position	–0.37	0.03 – 16.36	0.69	0.817
Blood transfusion (y)	3.95	4.15 – 656.46	52.21	0.002*
Estimated blood loss (mL)	0.001	0.997 – 1.005	1.001	0.594

ASA PS: American Society of Anesthesiologists Physical Status; β: unstandardized regression weight; CI: confident interval; F: female; M: male; y: yes.
* $p < 0.05$ is considered as statistically significant.

Medication use preceding surgery among the AIS patients

In regards to the five patients who devel-

oped AIS, two of the patients were on aspirin therapy, two of the patients were on clopidogrel therapy, and one patient was taking rivaroxaban. Both of the patients who were on aspirin therapy continued their regular doses of aspirin before their procedures. Of the two patients taking clopidogrel, one patient ceased clopidogrel five days pre-operatively and the other patient continued to take their usual dose of clopidogrel pre-operatively. The patient taking rivaroxaban ceased the rivaroxaban three days pre-operatively.

Discussion

The perioperative period is generally defined as the period from entry into the operating room to either hospital discharge or 30 days after surgery.[6] Most observational studies discussing perioperative AIS defined the perioperative period as within 30 days after surgical intervention.[3-5] In the last two decades, the implementation of enhanced recovery after surgery (ERAS) programs have significantly reduced hospital stay length by 0.5 – 3.5 days for non-cardiac surgeries.[7,8] Furthermore, a retrospective matched control study including 24,641 patients demonstrated that most of AIS events (53%) occurred within 24 hours after non-cardiac surgery, and only 16% of these events happened in postoperative days 7 to 30.[2] Therefore, this study defined the perioperative period as the time-period from operation to hospital discharge in an attempt to limit included AIS events to those that happened shortly after surgery.

Our study identified the overall incidence of perioperative AIS after non-cardiac, non-neurologic, and non-major vascular surgery to be of 0.01%. The incidence of perioperative AIS in our study is considerably lower than some previously reported studies,[3-5] as those studies defined the perioperative period as up to 30 days after surgery. As post-operative hospital stay lengths have significantly decreased following world-wide implementation of fast-track surgery protocols, the identification of risk factors for AIS shortly after surgery during the same hospital stay period could be more clinically pragmatic. Furthermore, the analysis of risk factors for AIS reported after hospital discharge could be confounded by other uncontrollable environmental or emotional factors. The overall in-hospital mortality rate of perioperative AIS was 16.7%, which is similar to the results reported by previous large cohort studies.[3,5] In addition, our study also measured the functional outcomes in AIS patients who survived to hospital discharge. We found that peri-operative AIS not only carried a high probability of in-hospital mortality, but all survivors developed moderate-to-severe disabilities after the event and required long-term post-stroke care. Our study suggests that the development of perioperative AIS may have an extremely high impact on the social and economic systems.

This study examined various risk factors for developing perioperative AIS, including patient characteristics, patient medical history and current medications, and surgical related and anesthesia-related factors. Compared with the matched controls, univariate analysis found that older age and current anti-platelet use were associated with increased risks of developing perioperative AIS. A multivariate analysis of potential patient factors confirmed that pre-operative antiplatelet therapy was a strong independent risk factor for developing peri-operative AIS with an AOR of 5.22 (95% CI 1.03 – 26.44; $p = 0.046$). Anti-platelet therapy is recommended to nearly all AIS patients that do not have contraindications and is also recommended for primary and secondary stroke prevention.[9] Therefore, it could be presumed that patients who were taking aspirin pre-operatively were already at higher risk of developing AIS.

Regarding surgical and anesthesia-related factors, our study found that patients who

underwent spinal surgery, especially surgeries performed in the prone position, were at higher risk of developing peri-operative AIS. Intra-operative blood loss and erratic blood pressures during surgery were also associated with higher incidences of peri-operative AIS. Following multivariate analysis, red blood cell transfusions were an independent risk factor for developing perioperative AIS, as blood transfusions can be considered a surrogate clinical indicator for intraoperative excessive blood loss and hemodynamic instability.[10,11] Spinal surgeries (posterior spinal fusion surgeries in particular) have been known to be associated with an increased risk of developing AIS up to 30 days post-operatively (incidence 0.13 – 0.44%).[12,13] However, our study did not find any significant differences (p = 0.064) in AIS incidence between spinal surgeries and other surgeries though multivariate analysis. Increased blood loss during spine surgery particularly in revision procedures or multilevel spinal fusion might significantly affect perioperative outcomes, as intraoperative blood loss > 500 mL is associated with up to 3.67 times greater odds of postoperative complications, including neurological deficits.[14]

Strengths and limitations

Our work provides important information that were not commonly reported in the literature regarding the development of perioperative AIS after low-risk surgeries. First, we identified the incidence of AIS during the index hospital stay period rather than the incidence within 30 days after surgery. Risk factor analysis of AIS events that occurred after hospital discharge can be confounded by other uncontrollable variables. In fact, clinical observational studies have found stroke incidence can increased 3.8 folds at 1 year after surgery.[12] Secondly, this chart-review study provided more detailed risk factors regarding peri-operative AIS development, including patients' regular medications, anesthesia techniques, intra-operative positioning, and intra-operative hemodynamic changes. Thirdly, we included the functional status and residual disability of the surviving patients in this analysis of perioperative AIS.

Our study also has some limitations. First, this study included only a small sample size of perioperative AIS patients. As AIS is a relatively rare event during perioperative period, this study could be underpowered in detecting significant differences with some of the potential risk factors, such as older age and spinal surgery. Second, only patients with obvious clinical neurological deficits were proceeded to imaging studies. Therefore, patients with covert AIS that presented with subtle or absence of neurological signs after surgery were not included in this study. Third, the retrospective study design limits the ability to establish any direct causal relationships between the perioperative AIS and the measured variables. Forth, this study demonstrated that patients who taking antiplatelet agents were associated with increased risk for developing perioperative AIS. However, our database was not able to address the effects of cessation or continuing antiplatelet therapy prior to surgery on the development of AIS during perioperative period.

Conclusions

Our observational study finds that the incidence of perioperative AIS after non-cardiac, non-neurologic and non-major vascular surgery was 0.01% with a high in-hospital mortality rate of 16.7%. The survivals of perioperative AIS were incurred by moderate-to-severe functional impairment on hospital discharge. Patients who taking regular antiplatelet therapy and required RBC transfusion during operation, particularly spine surgery were associated with higher risks for perioperative AIS.

Author Contributions

Study Design, Chih-Tung Huang and

Sheng-Han Lin; Data Collection, Chih-Tung Huang; Statistical Analysis, Tzu-Shan Chen; Data Interpretation, Tzu-Shan Chen; Manuscript Preparation, Chih-Tung Huang; Literature Search, Chih-Tung Huang. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

This study was approved by the institutional review board of the E-Da Hospital, Kaohsiung, Taiwan (approval number EMRP-110-057). All procedures in this study were conducted in accordance with the institutional ethical standards and with the 1964 Helsinki declaration and its later amendments.

Informed Consent Statement

Informed written consent from patients was waived.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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