Impact of perioperative acute ischemic stroke on the outcomes of noncardiac and nonvascular surgery: a single centre prospective study

Murat Biteker, MD*
Kadir Kayatas, MD†
Funda Muserref Türkmen, MD†
Cemile Handan Mısırlı, MD‡

From *Istanbul Medipol University, Faculty of Medicine, Department of Cardiology, Istanbul, Turkey, †Haydarpasa Numune Education and Research Hospital, Department of Internal Medicine, Istanbul, Turkey, and the ‡Haydarpasa Numune Education and Research Hospital, Department of Neurology, Istanbul, Turkey

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Correspondence to:
M. Biteker
Bankalar Caddesi, Horoz Apt, 4/7
Cevizli/Kartal, Istanbul, Turkey
murbit2@yahoo.com

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Background: Although ischemic stroke is a well-known complication of cardiovascular surgery it has not been extensively studied in patients undergoing noncardiac surgery. The aim of this study was to assess the predictors and outcomes of perioperative acute ischemic stroke (PAIS) in patients undergoing noncardiothoracic, nonvascular surgery (NCS).

Methods: We prospectively evaluated patients undergoing NCS and enrolled patients older than 18 years who underwent an elective, non-daytime, open surgical procedure. Electrocardiography and cardiac biomarkers were obtained 1 day before surgery, and on postoperative days 1, 3 and 7.

Results: Of the 1340 patients undergoing NCS, 31 (2.3%) experienced PAIS. Only age (odds ratio [OR] 2.5, 95% confidence interval [CI] 1.01–3.2, $p < 0.001$) and preoperative history of stroke (OR 3.6, 95% CI 1.2–4.8, $p < 0.001$) were independent predictors of PAIS according to multivariate analysis. Patients with PAIS had more cardiovascular (51.6% v. 10.6%, $p < 0.001$) and noncardiovascular complications (67.7% v. 28.3%, $p < 0.001$). In-hospital mortality was 19.3% for the PAIS group and 1% for those without PAIS ($p < 0.001$).

Conclusion: Age and preoperative history of stroke were strong risk factors for PAIS in patients undergoing NCS. Patients with PAIS carry an elevated risk of perioperative morbidity and mortality.

Contexte : Même si l'AVC ischémique est une complication bien connue de la chirurgie cardiovasculaire, elle n'a pas fait l'objet d'études approfondies chez les patients soumis à une chirurgie non cardiaque. Le but de cette étude était d'évaluer les prédicteurs et les conséquences de l'AVC ischémique aigu périopératoire (IAPO) chez des patients soumis à une chirurgie non cardiothoracique et non vasculaire (NCNV).

Méthodes : Nous avons évalué de manière prospective les patients soumis à une chirurgie NCNV et inscrit les patients de plus de 18 ans qui subissaient une intervention chirurgicale ouverte non urgente nécessitant une hospitalisation. L'électrocardiogramme et les biomarqueurs cardiaques étaient obtenus 1 jour avant la chirurgie et aux jours 1, 3 et 7 suivant la chirurgie.

Résultats : Parmi les 1340 patients soumis à une chirurgie NCNV, 31 (2,3 %) ont présenté un AVC IAPO. Seuls l'âge (rapport des cotes [RC] 2,5, intervalle de confiance [IC] de 95 % 1,01–3,2, $p < 0,001$) et des antécédents préopératoires d'AVC (RC 3,6, IC de 95 % 1,2–4,8, $p < 0,001$) ont été des prédicteurs indépendants de l'AVC IAPO selon l'analyse multivariée. Les patients victimes d'un AVC IAPO avaient davantage de complications cardiovasculaires (51,6 % c. 10,6 %, $p < 0,001$) et non cardiovasculaires (67,7 % c. 28,3 %, $p < 0,001$). La mortalité perhospitalière a été de 19,3 % dans le groupe victime d'AVC IAPO et de 1 % chez les patients indemnes d'AVC IAPO ($p < 0,001$).

Conclusion : L'âge et les antécédents préopératoires d'AVC sont des facteurs de risque importants à l'égard de l'AVC IAPO chez les patients soumis à une chirurgie NCNV. Les patients victimes d'un AVC IAPO sont exposés à un risque élevé de morbidité et de mortalité périopératoires.

Perioperative acute ischemic stroke (PAIS) is devastating to both patients and physicians, particularly when PAIS develops postsurgery in patients with no evidence of cerebrovacsular dysfunction preoperatively. The incidence of PAIS ranges from 0.05% after general surgery to 9% after cardiac surgery and carotid endarterectomy, and PAIS has been associated with substantial perioperative morbidity and mortality.[1–10] Cardiopulmonary bypass and carotid endarterectomy induce unique pathophysiology in patients undergoing cardiovascular surgery, and it is inappropriate to assume that the risk factors for PAIS after noncardiac and nonvascular surgery are the same as those after cardiac or aortic surgery. Several investigators have reported the incidence and risk factors for PAIS among noncardiac surgery patients.[11–13] Although PAIS has been reported in approximately 0.08%–3.5% of patients, these figures likely underestimate the true incidence of PAIS owing to inconsistent definition criteria, retrospective study design and the use of an administrative database. A number of risk factors for PAIS, including renal disease, atrial fibrillation, hypertension, prior stroke, valvular disease, congestive heart failure, carotid disease and history of tobacco use, have been identified in these studies. However, relatively few data are available regarding the effect on the cardiac and noncardiac outcome of perioperative PAIS for these surgeries. We performed a prospective study in a cohort of patients undergoing noncardiac and nonvascular surgery to determine incidence, risk factors and outcome of PAIS.

Methods

Study group

After institutional ethics approval, we prospectively obtained data on consecutive adult (≥ 18 yr) patients undergoing noncardiothoracic and nonvascular surgery at Haydarpasa Numune Education and Research Hospital between January 2010 and March 2012.

The collection of patient data included patient age, sex, body mass index (BMI), preoperative medications, American Society of Anesthesiologists (ASA) physical status[14] and comorbidities. We used the Revised Cardiac Risk Index (RCRI) for prediction of cardiac risk based on 6 prognostic factors: high-risk type of surgery (defined as intraperitoneal, intrathoracic, or suprainguinal vascular procedures), ischemic heart disease, congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes and preoperative serum creatinine greater than 176.8 μmol/L (2.0 mg/dL).[15] Each of the prognostic factors was assigned 1 point. Anesthetic management, monitoring and other aspects of perioperative management were at the discretion of the attending physician. Electrocardiography and cardiac biomarkers (creatine kinase-MB and troponin I) were evaluated 1 day before surgery, immediately after surgery and on postoperative days 1, 3 and 7. Standard transthoracic echocardiography was performed in all patients using Vivid Three System (Vivid 3 pro, GE Vingmed) before surgery. We measured left ventricle ejection fraction using a modified Simpson rule. Standard, 2-dimensional M-mode and Doppler echocardiographic measurements were obtained for all patients.

The left atrial dimension was measured at end-ventricular systole in the parasternal long axis view according to the American Society of Echocardiography (ASE) recommendations.[16] The severity of valvular regurgitation and stenosis was also graded according to the ASE recommendations.[17,18] Patients who had any type of rheumatic, myxomatous, ischemic or degenerative valve disease with moderate or greater valve regurgitation and/or stenosis were classified as having heart valve disease.

Patients presenting for surgery who required only local or monitored anesthesia care and who were having daytime surgical procedures were excluded from our analysis. Emergent surgical cases, patients with an ASA classification of 5 (moribund, not expected to live 24 h irrespective of operation) and patients with prosthetic heart valves were also excluded. Vascular and intrathoracic surgeries are not performed in our institution. We included patients undergoing major gastrointestinal surgery (i.e., laparotomy, advanced bowel surgery, gastric surgery), major gynecological cancer surgery (i.e., abdominal hysterectomy, oophorectomy), major open or transurethral urological surgery (i.e., cystectomy, radical nephrectomy, total prostatectomy), head and neck surgery and hip or knee arthroplasty. Cardiac risk assessment, preoperative preparation, drug therapy and postoperative follow-up were completed according to current American College of Cardiology/American Heart Association guidelines.[19] Patients were followed until discharge after surgery.

Study outcomes

The primary outcome evaluated was PAIS. Secondary outcomes included major cardiovascular and noncardiovascular complications, all-cause mortality and length of postoperative stay in hospital. Acute ischemic stroke was defined as rapidly developing clinical signs of focal disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.[20] A focal disturbance lasting less than 24 hours was classified as a transient ischemic attack. The perioperative cardiovascular events were defined as the occurrence of severe arrhythmias requiring treatment, acute heart failure, acute coronary syndrome (i.e., nonfatal acute myocardial infarction or unstable angina), pulmonary thromboembolism, peripheral arterial thromboembolism and nonfatal cardiac arrest. Perioperative myocardial infarction was defined according to the universal definition of myocardial infarction.[21] The diagnosis of peripheral arterial embolism was based on clinical, laboratory and radiological findings signifying vascular occlusion with renal, intestinal or limb ischemia.

Noncardiovascular complications were lobar pneumonia confirmed by chest radiograph and requiring antibiotic therapy, respiratory failure requiring intubation for more than 2 days or reintubation, wound infection, bacteremia, acute kidney injury and major and minor bleeding. Acute kidney injury was defined based on the RIFLE (risk, injury, failure, loss of function, end-stage kidney disease) criteria using the maximal change in serum creatinine and estimated glomerular filtration rate during the first 7 postoperative days compared with preoperative baseline values.[22] We estimated the glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula.[23]

Major bleeding was defined as fatal or life-threatening bleeding at a critical location (i.e., retroperitoneal, intracranial, intraocular, intraspinal), requiring surgical intervention or administration of at least of 2 units of packed red blood cells. Minor bleeding was defined as all other reported bleeding events not meeting the criteria for a major bleed that did not require hospital admission or transfusion.

Table 1. Preoperative characteristics of the patients

Characteristic	Group; no. (%)*			*p* value
	All patients, *n* = 1340	PAIS, *n* = 31	No PAIS, *n* = 1309	
Age, mean ± SD, yr	65.81 ± 13.97	71.58 ± 12.42	65.236 ± 11.73	< 0.001
Sex, male	712 (53.1)	20 (64.5)	692 (52.9)	0.20
Body mass index, mean ± SD	28.28 ± 10.42	28.12 ± 11.60	27.99 ± 10.81	0.77
Medical history				
Current smoking	166 (12.4)	3 (9.7)	163 (12.6)	0.41
Diabetes mellitus	335 (25)	13 (41.9)	322 (24.6)	0.028
Hypertension	742 (55.4)	22 (71)	720 (55)	0.08
Hyperlipidemia	498 (37.2)	12 (38.7)	486 (37.4)	0.79
Heart failure	147 (11)	14 (45.2)	133 (10.2)	< 0.001
Coronary artery disease	358 (26.7)	12 (38.7)	346 (26.4)	0.13
History of cerebrovascular disease	105 (7.8)	8 (25.8)	97 (7.4)	< 0.001
Chronic obstructive pulmonary disease	151 (11.3)	3 (9.7)	148 (11.3)	0.35
Malignancy	226 (16.9)	4 (12.9)	221 (16.9)	0.56
Chronic renal failure	103 (7.7)	4 (12.9)	99 (7.6)	0.27
Atrial fibrillation	206 (15.4)	17 (54.8)	189 (14.4)	< 0.001
New York Heart Association functional class				
1	825 (61.6)	13 (41.9)	812 (62)	
2	476 (35.5)	17 (54.8)	459 (35.1)	0.07
3	39 (2.9)	1 (3.2)	38 (2.9)	
4				
Revised cardiac risk index				
0	178 (13.3)	1 (3.2)	177 (13.5)	
1	599 (44.7)	5 (16.1)	594 (45.4)	< 0.001
2	380 (28.4)	10 (32.3)	370 (28.3)	
3	166 (12.3)	14 (45.2)	152 (11.6)	
4	17 (1.3)	1 (3.2)	16 (1.2)	
ASA status				
ASA I	216 (16.1)	2 (6.5)	214 (16.4)	
ASA II	677 (50.5)	7 (22.6)	670 (51.2)	< 0.001
ASA III	334 (24.9)	13 (41.9)	321 (24.5)	
ASA IV	113 (8.4)	9 (29.0)	104 (7.9)	
Laboratory tests, mean ± SD				
C-reactive protein, nmol/L	181.9 ± 322.9	281.9 ± 376.2	181.0 ± 320.0	0.06
Mean platelet volume, fL	8.55 ± 6.21	8.83 ± 5.94	8.51 ± 6.38	0.76
Hemoglobin, g/L	123.0 ± 18.0	122.0 ± 17.5	124.0 ± 19.0	0.60
White blood count, $\times 10^9$/L	8.55 ± 4.93	8.81 ± 3.11	8.58 ± 5.11	0.83
Fasting glucose, mmol/L	6.53 ± 2.10	7.14 ± 2.17	6.15 ± 2.09	0.003
Creatinine, μmol/L	95.47 ± 114.04	108.73 ± 122.88	91.05 ± 109.62	0.43
Albumin, g/L	38.0 ± 5.9	37.3 ± 6.4	38.3 ± 5.8	0.35
Echocardiography				
Left ventricle ejection fraction mean ± SD, %	57.9 ± 9.8	50.6 ± 12.9	58.7 ± 8.5	< 0.001
Left atrium diameter, mean ± SD mm	37.1 ± 4.8	39.9 ± 6.1	36.8 ± 4.9	< 0.001
Pulmonary artery systolic pressure, mean ± SD mm Hg	27.7 ± 9.8	29.9 ± 10.5	27.2 ± 9.7	0.18
Valvular heart disease	127 (9.5)	7 (22.6)	120 (9.2)	< 0.001

ASA = American Society of Anesthesiologists; PAIS = perioperative acute ischemic stroke; SD = standard deviation.
*Unless otherwise indicated.

Statistical analysis

Data were analyzed using SPSS for Windows version 15 (SPSS Inc). The continuous variables are expressed as means ± standard deviations, and we compared these variables between the groups using a 2-tailed Student *t* test. We performed nonparametric tests (Mann–Whitney *U* test) when appropriate. We used the Fisher exact and χ^2 tests to compare categorical variables. We considered results to be significant at $p < 0.05$.

RESULTS

Preoperative characteristics

A total of 1340 patients (mean age 65.8 ± 14 yr) underwent noncardiothoracic, nonvascular surgery during the study period. The incidence of PAIS in the study cohort was 31 of 1340 (2.3%). Of the 31 patients with PAIS, 23 had a stroke and 8 had a transient ischemic attack. The baseline clinical, demographic, laboratory and echocardiographic

Table 2. Perioperative characteristics

Characteristic	Group; no. (%)			*p* value
	All patients, *n* = 1340	PAIS, *n* = 31	No PAIS, *n* = 1309	
Type of surgery				0.24
General	558 (41.6)	12 (38.7)	546 (41.7)	
Urological	273 (20.3)	6 (19.4)	267 (20.4)	
Plastics	75 (5.6)	2 (6.5)	73 (5.6)	
Gynecological	74 (5.5)	3 (9.7)	71 (5.4)	
Orthopedic	306 (22.8)	6 (19.4)	300 (22.9)	
Neurological	38 (2.8)	1 (3.2)	37 (2.8)	
Ear/nose/throat	16 (1.2)	1 (3.2)	15 (1.1)	
Preoperative medications				
Angiotensin-converting enzyme inhibitor	431 (32.2)	13 (41.9)	418 (31.9)	0.24
β-blocker	306 (22.8)	7 (22.6)	299 (22.8)	0.97
Statin	130 (9.7)	1 (3.2)	129 (9.9)	0.22
Aspirin	348 (25.9)	11 (35.5)	337 (25.7)	0.22
Calcium inhibitor	199 (14.8)	4 (12.9)	195 (14.9)	0.76
Diuretics	87 (6.5)	2 (6.4)	85 (6.5)	0.98

PAIS = perioperative acute ischemic stroke.

Table 3. Association of perioperative acute ischemic stroke with adverse perioperative outcomes

Characteristic	Group; no. (%)*			*p* value
	All patients, *n* = 1340	PAIS, *n* = 31	No PAIS, *n* = 1309	
Cardiovascular complications	155 (11.6)	16 (51.6)	139 (10.6)	< 0.001
Acute coronary syndrome	40 (3)	5 (16.1)	35 (2.7)	< 0.001
Acute heart failure	34 (2.5)	2 (6.5)	32 (2.4)	0.23
Severe arrhythmia	29 (2.2)	4 (12.9)	25 (1.9)	< 0.001
Pulmonary embolism	18 (1.3)	2 (6.5)	16 (1.2)	0.13
Nonfatal cardiac arrest	12 (0.9)	2 (6.5)	10 (0.8)	0.003
Arterial thromboembolism	22 (1.6)	1 (3.2)	21 (1.6)	0.22
Noncardiovascular complications	391 (29.2)	21 (67.7)	370 (28.3)	< 0.001
Wound infection	85 (6.3)	7 (22.6)	78 (6)	< 0.001
Respiratory failure	15 (1.1)	2 (6.5)	13 (1)	0.030
Lobar pneumonia	24 (1.8)	3 (9.7)	21 (1.6)	0.021
Bacteremia	14 (1)	2 (6.5)	12 (0.9)	0.024
Minor bleeding	124 (9.2)	4 (12.9)	120 (9.2)	0.20
Major bleeding	38 (2.8)	1 (3.2)	37 (2.8)	0.60
Acute kidney injury	91 (6.8)	2 (6.5)	89 (6.8)	0.72
Length of stay, mean ± SD d	8.3 ± 8.1	11.4 ± 9.5	8.4 ± 7.7	< 0.001
Mortality	18 (1.4)	6 (19.3)	13 (1)	< 0.001

PAIS = perioperative acute ischemic stroke; SD = standard deviation.
*Unless otherwise indicated.

characteristics are summarized in Table 1, and perioperative characteristics are presented in Table 2. The 2 groups were comparable in terms of sex, tobacco use, BMI, chronic obstructive pulmonary disease, hypertension, hyperlipidemia, chronic renal failure, preoperative cardiac medication and type of surgical procedure.

Predictors of PAIS

Compared to patients without PAIS, those with PAIS were older and more often had diabetes (41.9% v. 24.6%, $p = 0.028$), heart failure (45.2% v. 10.2%, $p < 0.001$), history of cerebrovascular disease (25.8% v. 7.4%, $p < 0.001$) and atrial fibrillation (54.8% v. 14.4%, $p < 0.001$). They also had higher preoperative ASA class and RCRI scores (Table 1). Compared to patients without PAIS, those who had PAIS had higher left atrium dimensions and reduced left ventricle ejection fraction. They were also more likely to have valvular heart disease at presentation. Univariate analysis revealed that the age, atrial fibrillation, diabetes, heart failure, valvular heart disease, history of cerebrovascular disease, higher ASA and RCRI scores, increased fasting glucose levels, lower left ventricle ejection fraction and greater left atrial diameter were significantly associated with PAIS. However, on multivariate logistic regression analysis, only age (odds ratio [OR] 2.5, 95% confidence interval [CI] 1.01–3.2, $p < 0.001$) and preoperative history of stroke (OR 3.6, 95% CI 1.2–4.8, $p < 0.001$) were independent predictors of PAIS.

Effect of PAIS on outcome

In-hospital perioperative adverse events and postoperative length of stay data are summarized in Table 3. Postoperative length of stay was prolonged in patients who experienced PAIS (11.4 ± 9.5 v. 8.4 ± 7.7 d, $p < 0.001$). The most common cardiovascular complications were acute coronary syndrome, acute heart failure and arrhythmia, and the most common noncardiac complications were minor bleeding, wound infection and lobar pneumonia. Patients with PAIS had significantly higher rates of cardiovascular (51.6% v. 10.6%, $p < 0.001$) and noncardiovascular complications (67.7% v. 28.3%, $p < 0.001$) than those without PAIS (Fig. 1). Patients with perioperative PAIS also had a greater incidence of in-hospital mortality than those without PAIS (19.3% v. 1%, $p < 0.001$). After adjustment for age, sex, comorbidities and clinical risk indicators, multivariate analysis showed that PAIS was a significant independent predictor for cardiovascular adverse events (OR 2.87, 95% CI 1.10–5.43, $p < 0.001$), noncardiovascular complications (OR 1.56, 95% CI 1.15–3.36, $p < 0.001$), and in-hospital mortality (OR 3.92, 95% CI 1.24–10.40, $p < 0.001$).

Discussion

The incidence of PAIS among adult patients undergoing noncardiac and nonvascular surgery in our study was 2.3%, and PAIS remains a devastating complication following surgery.

The reported incidence of PAIS following noncardiac surgery procedures varies from 0.05% to 7%, depending on the definition of this complication, diagnostic tests, duration of follow-up, study design and the composition of studied populations.[24] Previous studies, most of which included a large proportion of cardiac and vascular surgery patients, have identified several risk factors for the development of PAIS after surgery, including advanced age, impaired left ventricular function, long cardiopulmonary bypass time, preoperative renal failure, history of stroke, diabetes and emergent procedures.[25–30] However, incidence, predictors and outcome of PAIS in patients undergoing noncardiac and nonvascular surgery are not well studied. Furthermore, most of the previous and current studies are retrospective reviews of administrative databases, and transient ischemic attacks are usually missed owing to inaccurate coding. Kikura and colleagues[31] retrospectively evaluated 36 634 consecutive

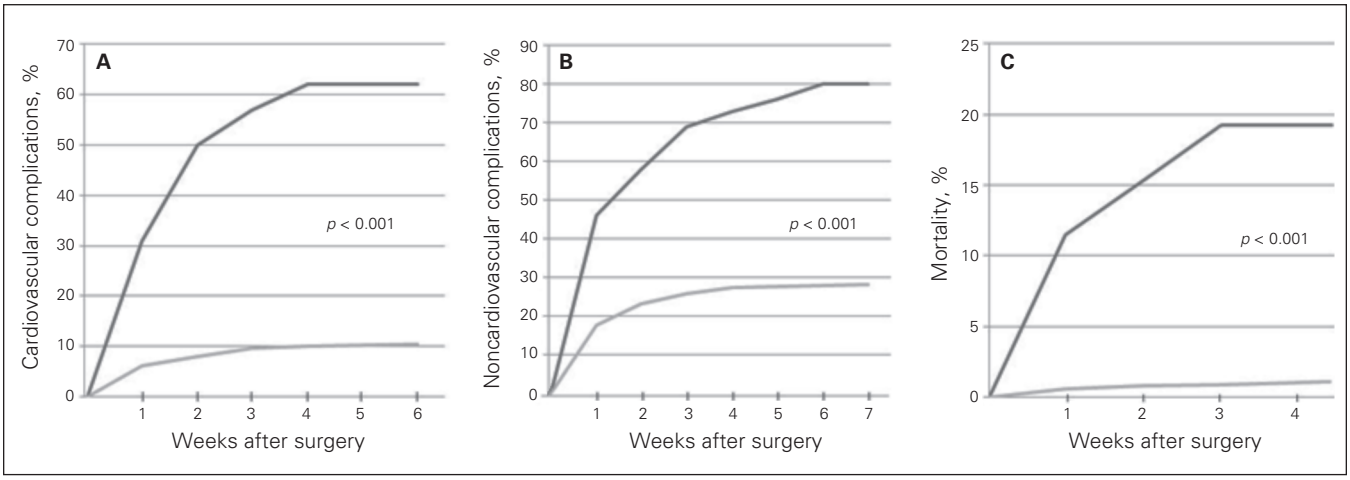

Fig. 1. Kaplan–Meier curves for the **(A)** cardiovascular complications, **(B)** noncardiovascular complications and **(C)** in-hospital mortality after noncardiac, nonvascular surgery in patients (black line) with and (grey line) without perioperative acute ischemic stroke.

patients after elective noncardiac, noncarotid surgery. Acute stroke occurred in 126 (0.34%) patients during the first 30 days after surgery. Older age and female sex were independent predictors of postoperative stroke. In a retrospective study, Popa and colleagues[32] tried to determine the predictors of ischemic stroke in patients aged 65 years and older undergoing hip operations. A total of 1606 patients underwent 1886 hip procedures between 1988 and 2002 and were observed for ischemic stroke for 1 year after their procedure. The rate of stroke at 1 year after hip surgery was 3.9%. In multivariate analysis, history of stroke and hip fracture repair were predictors of postoperative stroke. In another retrospective administrative database study, Bateman and colleagues[33] reported an incidence of perioperative stroke of 0.7% after hemicolectomy, 0.2% after hip replacement and 0.6% after lobectomy or segmental lung resection; the incidence increased to 1.0%, 0.3% and 0.8%, respectively, in patients aged 65 years or older. The authors found 4 independent predictors for perioperative stroke: atrial fibrillation, history of stroke, cardiac valvular disease and renal disease. They also showed that PAIS has a profoundly deleterious effect on outcome after surgery, greatly increasing the odds of in-hospital mortality and decreasing the number of hospital-free days. Mashour and colleagues[34] presented an analysis of the prospectively collected American College of Surgeons National Surgical Quality Improvement Program database. The authors investigated perioperative stroke in more than 523 000 patients undergoing noncardiac, nonneurologic surgery. They found that the overall incidence of stroke was 0.1% and that perioperative stroke led to an 8-fold increase in 30-day mortality. In another prospective, multicentre study of patients undergoing surgical procedures under general or regional anesthesia in 23 hospitals, Sabaté and colleagues[35] investigated major adverse cardiac and cerebrovascular events in 3387 patients and found that the incidence of stroke was 0.4%. The higher PAIS incidence found in the present study versus that reported in the aforementioned studies could be explained by the prospective design of the study, accurate determination of transient ischemic attacks and greater prevalence of comorbidities, such as diabetes, heart failure, atrial fibrillation and history of stroke, in our patients.

A unique finding of our study was that the development of PAIS was associated not only with increased in-hospital mortality and prolonged length of stay in hospital, but also with increased incidence of different types of cardiovascular and noncardiovascular adverse events, such as nonfatal cardiac arrest, acute heart failure, wound infection, lobar pneumonia and respiratory failure. This could be explained in part by the older age and greater prevalence of preoperative comorbidities in patients with PAIS and in part because of the prolonged length of stay for these patients.

Limitations

Although our cohort included a heterogeneous group of patients and procedures, it reflected the practice and outcomes at a single institution and may not be replicable in other settings. Patients undergoing emergent surgery, high-risk surgery (i.e., vascular surgery) and cardiothoracic surgery were not included. Because long-term follow-up after discharge was not performed, the incidence of complications developing after discharge may have been underestimated. Our study cannot establish a causal relation between PAIS and cardiac or noncardiac complications.

Conclusion

Perioperative PAIS is associated with prolonged length of stay in hospital, increased cardiovascular and noncardiovascular adverse events and in-hospital mortality in this cohort of patients undergoing noncardiothoracic, nonvascular surgery. Evaluating the risk:benefit ratio, particularly for elderly patients with a history of stroke or transient ischemic attack, before surgery is essential to optimize care. Physicians must implement diagnostic, therapeutic and procedural measures to modify the perioperative risk to prevent stroke and minimize morbidity.

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Contributors: All authors designed the study. M. Biteker acquired and analyzed the data, which K. Kayatas, F.M. Türkmen and C.H. Misirli also analzed. M. Biteker wrote the article, which all authors reviewed and approved for publication.

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