Cerebral Artery Stenosis as a Risk Factor for Post-operative Cognitive Dysfunction

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ABSTRACT

Objective: The reasons for post-operative cognitive decline (POCD) remain largely unknown. Therefore, we determined the effect of cerebral artery stenosis on post-operative cognitive function in the elderly.

Methods: Eligible patients were between 60 and 80 years of age, and underwent elective, non-cardiac surgery at Beijing Friendship Hospital (Capital Medical University, Beijing, China) in 2013. Neuropsychological tests and transcranial Doppler ultrasound (TCD) were performed in 120 subjects pre-operatively. According to the results of TCD, patients were consecutively enrolled into the following three groups: normal (Group I), sclerosis (Group II); and narrow (Group III). The diagnosis of POCD was based on the criteria of the International Study of Postoperative Cognitive Dysfunction (ISPOCD) group. Neuropsychological testing was repeated 7 days post-operatively.

Results: A total of 95 patients completed the post-operative assessment on day 7. The incidence of POCD in Groups I, II, and III was 16.2%, 27.5%, and 55.6%, respectively. The incidence of POCD was significantly higher in Group III than Group I. Logistic stepwise regression analysis demonstrated that the peri-operative risk factors for POCD were cerebral artery stenosis, the operative time, and time to awakening.

Conclusion: Cerebral artery stenosis may increase the incidence of POCD in the elderly.

Keywords: Cerebral artery stenosis, cognitive testing, post-operative cognitive decline, transcranial Doppler ultrasound

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INTRODUCTION

Post-operative cognitive dysfunction or decline (POCD) is an increasingly recognized phenomenon after major surgery (1). POCD is associated with impaired daily functioning (2) and increased morbidity and mortality (3). Although peri-operative safety has been substantially improved by advances in medical technology, a significant reduction in the incidence of POCD has not been achieved. POCD is detrimental to the quality of life, and increases medical costs and the social burden. Previous studies have led to the identification of old age as one of the major risk factors for long-term POCD; however, the etiology of POCD remains largely unknown.

POCD is primarily observed in the elderly. It has been reported that POCD is more frequent in patients > 65 years of age, with the reported incidence ranging from 3%-61% (4). POCD is a multifactorial syndrome influenced by each individual’s susceptibility, as well as various aspects of hospitalization and surgery. Risk factors for POCD include age, surgical complications, visual impairment, cognitive impairment, depression, poor organ function, narcotic use, surgical trauma, post-operative pain, and sleep disorders(5). It has been reported that elderly patients with a history of stroke have a significantly higher incidence of POCD (6). The purpose of the present study was to determine the effects of the pre-operative cerebral vascular status of patients on the incidence of POCD.

Transcranial Doppler ultrasound (TCD) is often used for the clinical detection of cerebral vascular conditions or diseases. The direction and velocity of blood flow, and the shape of the spectrum and audio frequency of the transcranial arteries, can accurately reflect cerebral artery stenosis, sclerosis, spasm, and ischemia, as well as other pathologic conditions(7). By ascertaining the scope of the pathologic changes, hemodynamic changes in the cerebral circle of Willis and its branches can be examined, thus providing a more objective and precise basis for diagnosis. TCD technology is characterized by no trauma, no radiation, good reproducibility, and high practicality, and TCD is well-accepted by patients. Furthermore, TCD has high specificity for the diagnosis of intracranial vessel stenosis, thus enabling reliable differentiation from other diseases. As a result, all patients in the current study underwent neuroimaging with TCD.

SUBJECTS AND METHODS

The study protocol was approved by the Ethics Committee of Beijing Friendship Hospital. Written informed consent was obtained from all participants.

Study population

Eligible patients had an American Society of Anesthesiologists (ASA) physical health status of II or III, were between 60 and 80 years of age, and had undergone elective non-cardiac surgery using isoflurane anesthesia at the Beijing Friendship Hospital. Exclusion criteria were as follows: 1) existing cognitive impairment, as evidenced by a Mini-Mental State Examination (MMSE) score < 23 (of 30 possible points) at the initial visit; 2) a history of alcoholism, drug dependence, or psychiatric or neurologic diseases (e.g., Alzheimer's disease or psychosis); (3) a severe visual or auditory disorder; (4) a history of surgery or anesthesia in the year before study enrollment; and (5) unwillingness to comply with the protocol or procedures.

Cognitive tests

The diagnosis of POCD was based on the criteria of the International Study of Postoperative Cognitive Dysfunction (ISPOCD) group. Neuropsychological tests were conducted pre-operatively and 7 days post-operatively. The cognitive tests took approximately 50 min, and were administered in a quiet environment with only the subject and investigator present. The cognitive tests included the Hopkins Verbal Learning Test-Revised (HVLT-R), the Brief

Visuospatial Memory Test-Revised (BVMT-R), the Benton Judgment of Line Orientation (JLO) Test, the Digit Span Test, the Symbol-Digit Modalities Test, the HVLT-R Delayed Recall Test, the HVLT-R Recognition Discrimination Index, the BVMT-R Delayed Recall Test, the BVMT-R Recognition Discrimination Index, the Trail Making Test, and the Verbal Fluency Test. The "change" score in each of the cognitive tests was obtained by subtracting the raw score of the baseline pre-operative test from the raw score of the post-operative cognitive test. POCD was defined when four or more of the change scores were negative, and the absolute value of each of the changed scores was greater than one standard deviation (SD) of the baseline score of the same cognitive test from all patients. The one SD criterion was employed as described in previous studies.

TCD ultrasound diagnostic criteria

TCD was performed pre-operatively to determine the presence of intracranial artery stenosis, extracranial carotid artery stenosis, and cerebral arteriosclerosis, according to the following three sets of imaging criteria: 1. Intracranial artery stenosis--changes in blood flow velocity (anomalies of segmental blood flow velocity), blood flow spectrum features (high-intensity blood flow signal spectrum with symmetric distribution of swirl and turbulence around the baseline), and blood flow audio frequency (low- or high-key rough noise and musical or mechanical noise); 2. Extracranial internal carotid artery stenosis--blood flow velocity (the lesion-side extracranial internal carotid artery blood flow velocity, an abnormal increase that is 1.5-fold higher than the contralateral artery), blood flow spectrum features, and blood flow audio frequency; and 3. Cerebral arteriosclerosis--changes in spectrum image (the S2 peak is greater than the S1 peak and end diastolic blood flow velocity is reduced), changes in the vascular elasticity index, and high-impedance waveforms. According to the results of TCD, patients were consecutively enrolled into three groups, as follows: normal (Group I); sclerosis (Group II); and narrow (Group III).

Anesthesia procedure

All of the patients received general anesthesia and the Bispectral Index (BIS) was monitored to determine the relative depth of general anesthesia. The pre-operative medication was atropine (0.25 mg). General anesthesia was induced with 0.03 mg/kg of midazolam, 2-4 μg/kg of fentanyl, 0.3 mg/kg of etomidate, and 0.6-0.9 mg/kg of rocuronium. Patients were intubated when the BIS value was <60. Standard anesthesia care was applied, including the use of routine monitors with ECG, blood pressure, and oxygen saturation. General anesthesia was maintained with 0.1-0.15 μg/kg·min remifentanil and isoflurane. The isoflurane concentration was adjusted to maintain the BIS value near 50.

Statistics

All the results were entered into a computer. Data are expressed as the mean±SD or as frequencies (%). Statistical processing was performed with SPSS software (version 16.0; SPSS, Inc., Chicago, IL, USA). Data on the measured variables in the three groups, including age, body weight, height, years of education, surgical time, intra-operative remifentanil and rocuronium ammonia dosages, and the opening-eyes time cognitive rating, all had a normal distribution. Independent sample t-tests were used for statistical analysis. ANOVA was used for variables measured in the three groups, and the $\chi 2$ test was used for enumeration data, such as gender, type of surgery, and incidence. P-values <0.05 were considered to denote statistically significant differences. Logistic stepwise regression was used for multivariate analysis.

RESULTS

A total of 140 patients elected to have non-cardiac surgery under general anesthesia on the selected date. Patients were evaluated pre- and post-operatively, as shown in Figure 1.Table 1 displays the general pre-, intra-, and post-operative conditions of the 95 patients who completed the post-operative follow-up assessment. According to the results of TRC, 37 patients were normal, 40 had sclerosis, and 18 had stenosis. The sclerosis and stenosis groups were significantly older than the control group (P=0.001 and P=0.000, respectively). POCD was present in 6 (16.2%), 11 (27.5%), and 10 (55.6%) patients in the normal, sclerosis, and stenosis groups, respectively, with the normal group being significantly different from the stenosis group (P=0.003), but not the sclerosis group (P=0.172; Table 2). Multivariate logistic stepwise regression analysis revealed three POCD risk factors, as follows: the extent of cerebrovascular stenosis (P=0.043); operative time (P=0.005); and time to awakening (P=0.029; Table 3).

DISCUSSION

The pathogenesis of POCD has yet to be clarified. Currently, most researchers believe that the mechanism underlying POCD involves degenerative changes in the nervous system, which are induced or exacerbated by external factors, such as anesthesia and surgery(8). Thus, POCD is considered to be multifactorial. The higher incidence of POCD in patients with cerebrovascular disease may be associated with impaired cerebrovascular autoregulation and/or a predisposition to cerebral infarction. Carotid artery stenosis often co-exists with cerebral and coronary artery diseases, which could easily lead to a decline in the cerebral blood supply under conditions of reduced blood pressure, thus affecting brain function.

Aging is the only established risk factor for POCD. Therefore, this study included elderly patients between 60 and 80 years of age. Arterial blood pressure was maintained at the pre-operative basal level ± 25% during surgery, and the pulse oxygen saturation was > 90%. End-tidal (Et) CO_2 monitoring and intermittent arterial blood gas collection were used to prevent the occurrence of hypoxia, hypocapnia, or anemia. By implementing these measures, the impact of other factors on POCD was excluded as much as possible. There was no significant difference among the three groups in terms of intra-operative remifentanil and rocuronium dosage, the volume of blood loss, and the operative time, which also confirmed the comparability of the groups.

The advantages of BIS make it one of the most common methods for monitoring the depth of anesthesia. BIS enables lower doses of narcotic drugs to be used (9) and effectively reduces the incidence of intra-operative awareness. When the intra-operative BIS is maintained at < 60, the patient will not have awareness during surgery (10). The intra-operative BIS was kept at approximately 50 in this study.

We used TCD technology, which is characterized by convenience and low cost, to assess cerebrovascular vessels. TCD enables the main intra- and extra-cranial vessels and branches to be thoroughly examined, and vascular changes can be detected at an earlier stage than with cerebral angiography(7). TCD has functional features that are not possible with head CT and MRI. In particular, TCD is sensitive to characteristic spectrum changes during the early stages of cerebral arteriosclerosis, making TCD an irreplaceable tool for the early detection of cerebrovascular diseases.

In this study, MMSE was used to screen for cognitive function pre-operatively. Because of the simple design, straightforward administration and ability to cover multiple aspects of cognitive function, the MMSE remains the most influential screening tool for cognitive impairment, having been in use for > 30 years. Patients with a pre-operative MMSE ≤ 23 were excluded. A combination of (11) cognitive tests was administered, as recommended by the ISPOCD, to provide an extensive evaluation of immediate memory, delayed memory, visual-spatial orientation, analytical skills, attention, ability to work, learn and execute, semantic memory storage, verbal fluency, and summarization and classification abilities.

These tests are highly sensitive to different types of cognitive impairments and are widely used in the field of neuropsychology. Most studies consider MMSE to be a cognitive screening instrument and use the combined instruments for a comprehensive assessment (11-13).

The incidence of POCD in Group III was significantly higher than Group I, which indicates that cerebral vascular stenosis may lead to a decrease in cerebral blood supply during surgery, thus affecting brain function and increasing the likelihood of POCD. Multivariate logistic stepwise regression analysis also indicated that cerebrovascular stenosis is a risk factor for POCD. Two other risk factors were operative time and time to awakening.

This study showed that the operative risk factor was the operative time. A longer duration of surgery results in the need for more anesthetic agents, as well as greater trauma and stress, thus leading to a higher risk of brain dysfunction. Time to awakening was another risk factor for POCD. A long awakening time indicates that the patient is more sensitive to anesthetic agents, and the effects are prolonged, which may contribute to the development of POCD.

This study demonstrated that cerebral vascular stenosis may increase the incidence of POCD in elderly patients. Therefore, pre-operative cerebrovascular examinations, especially for elderly patients, may enable those at high risk for POCD to be identified.

CONCLUSION

In conclusion, cerebral artery stenosis was shown to be associated with an increased incidence of POCD. The operative time and time to awakening were also risk factors for POCD. A pre-operative TCD examination may facilitate prediction of POCD in the elderly.

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AUTHORS' NOTE

Min Wang and Li Zhang carried out the molecular genetic studies. Yu Zhen and Fengling Gao participated in the sequence alignment and drafted the manuscript. Jingdong Ke participated in the sequence alignment. Guannan Ding and Peng Dong participated in the design of the study and performed the statistical analysis. Fangxiao Hong and Ming Tian conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.The authors declare that they have no conflicts of interest.

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Table 1: Pre-, intra-, and post-operative condition of patients in the normal, sclerosis, and stenosis groups

	Normal (n=37)	Sclerosis (n=40)	Stenosis (n=18)
Age (years)	63.97±4.83	68.35±6.36**	71.82±5.39##
Height (cm)	166.78±7.92	167.78±7.91	163.06±7.21
Body weight (kg)	66.64±11.22	68.00±10.92	65.56±10.60
Education (years)	8.32±4.68	10.12±4.19	7.12±5.83
Volume of blood loss (ml)	193.2±333.8	160.8±225.3	309.4±390.1
Operative time (min)	177.6±96.7	161.8±74.8	194.4±82.9
Volume of crystalloid (ml)	1136.8±469.7	1191.3±406.0	1426.5±571.2
Volume of colloid (ml)	662.2±313.0	720.0±354.6	794.1±309.2
Lowest intra-operative hemoglobin (g/dl)	11.42±0.96	11.30±1.95	10.19±1.35
Rocuronium (μg/kg/min)	10.75±5.46	9.30±3.71	9.04±2.87
Remifentanil (μg/kg/min)	0.13±0.03	0.13±0.04	0.13±0.05

** There was a significant difference in age between the sclerosis and normal groups, P=0.001.

There was a significant difference in age between the stenosis and normal groups, P=0.000.

Table 2: Incidence of POCD in the normal, sclerosis, and stenosis groups (n=95)

		Non-POCD (n)	POCD (%)
Normal group (n=37)	6	31	16.2
Sclerosis group (n=40)	11	29	27.5
Stenosis group (n=18)	10	8	55.6**
Total (n=95)	27	68	28.4

** The incidence of POCD in the stenosis group was significantly higher than the normal group, P=0.003.

Table 3: Analysis of POCD risk factors

	S.E.	Wald	P-value	Exp(B)
Degree of cerebral vascular stenosis	0.631	4.113	0.043*	3. 594
Gender	0.919	2.069	0.150	0.267
Age	0.108	1.262	0.261	0.886
Volume of blood loss	0.001	2.371	0.124	0.998
History of cerebrovascular disease	0.736	0.566	0.452	1.740
Operative time	0.006	7.995	0.005**	1． 017
History of smoking	0.834	1.419	0.234	0.371
History of drinking	0.901	2.867	0.090	4.596
History of hyperlipemia	0.826	0.915	0.339	2.203
History of coronary heart disease	0.983	2.431	0.119	0.216
History of diabetes	0.883	2.146	0.143	3.645
Years of education	0.875	0.415	0.520	1.756
Hypertension	0.782	0.115	0.734	1.304
Time to awakening	0.036	4.749	0.029*	0.925
Constant	5.501	0.000	0.997	1.024

Multivariate logistic stepwise regression analysis *P<0.05, **P<0.01

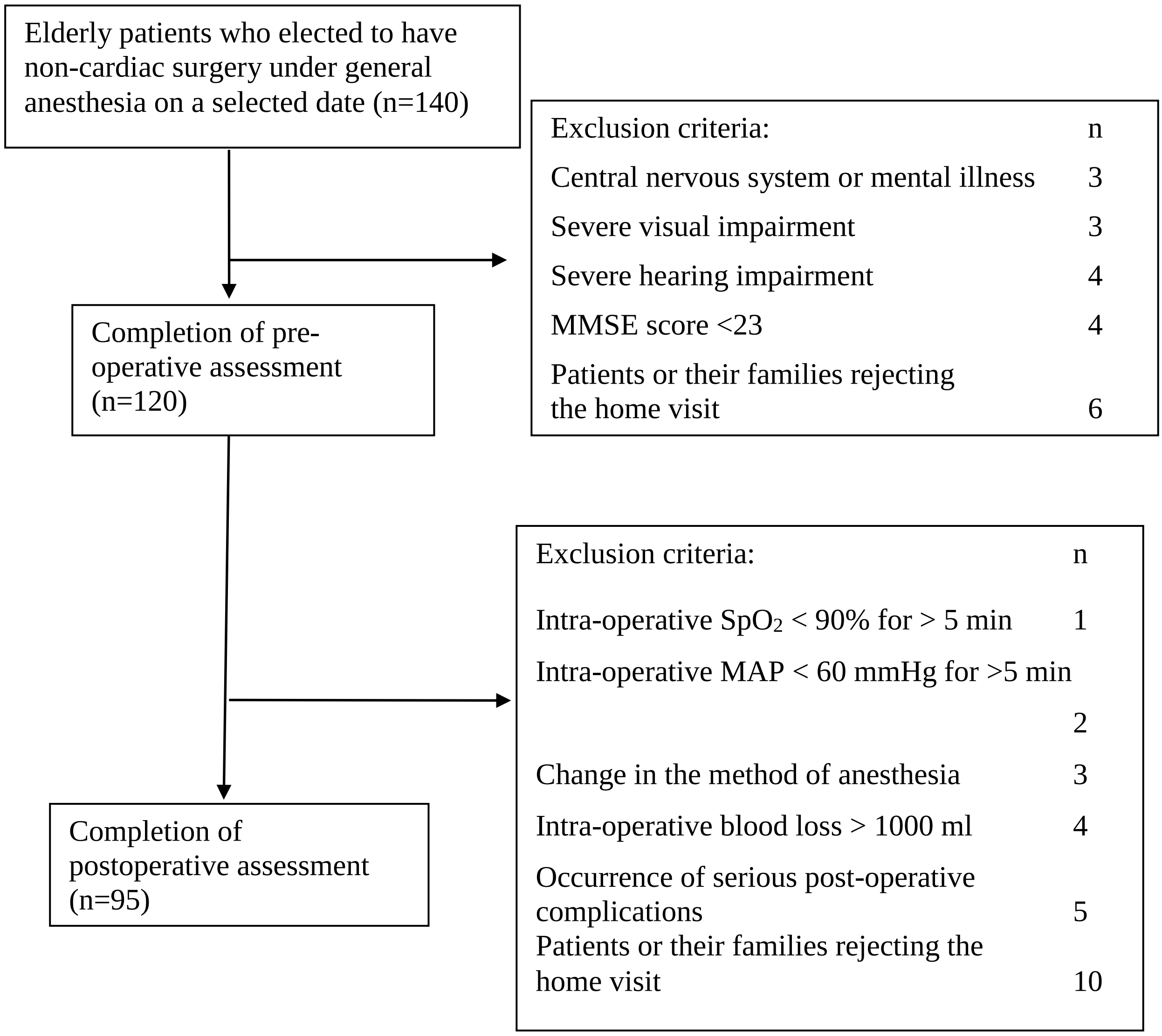

Fig 1: Experimental flow diagram.