Scholarly Journal of Psychology and Behavioral Sciences
DOI: 10.32474/SJPBS.2023.07.000255
ISSN: 2641-1768

Research Article

Cognitive Dysfunction Evaluation in Patients with Ruptured Anterior Communicating Aneurysm After Temporary Clipping

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Received: February 04, 2023 **Published:** February 13, 2023

Abstract

Aims: Cognitive dysfunction occurred after ruptured anterior communicating aneurysm (ACoA) surgery. Patients with temporary clipping of the A1 segment duration longer than 9 minutes are more likely to develop cognitive impairment. Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) are cognitive screening scales for cerebrovascular diseases, but their effect on assessing cognitive dysfunction after temporary clipping is not clear.

Method: Twenty-four volunteers (group A) were recruited as the baseline. Forty-five patients were chosen among ruptured ACoA cases who underwent early surgery within 72 hours. Of the 45 patients, 21 patients with temporary occlusion time shorter than 9 minutes (Group B), whereas temporary occlusion time equal or longer than 9 minutes in 24 patients (Group C). All the patients were under MMSE and MoCA evaluation 6 and 12 months post-surgery compared with the volunteers.

Results: The mean duration of temporary A1 occlusion for Group B is 7.43±0.81 minutes, whereas 11.00±2.11 minutes in Group C. MMSE total scores showed significant decrease both in Group B and C. MoCA total scores showed significant decrease in Group C, but not in Group B. Group B showed cognitive improvement in MMSE and MoCA, whereas Group C showed improvement in MoCA.

Conclusions: Our study shows that the MMSE and MoCA could evaluate cognitive impairment after temporary clipping in ACoA surgery. Cognitive dysfunction showed improvement when the temporary occlusion time was less than 9 minutes. Surgeons should shorten temporary clipping time in clinical practice, which greatly improves patients' prognostic cognitive function.

Keywords: Anterior communicating aneurysm; cognitive dysfunction; microsurgery; temporary clipping

Abbreviations: ACoA: Anterior Communicating Aneurysm; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; WCST: Wisconsin Card Sorting Test; CT: Computer Tomography; PE: Perseverative Errors; NPE: Nonperseverative Errors; SAH: Subarachnoid Hemorrhage; MRI: Magnetic Resonance Imaging.

Introduction

Craniotomy micro clipping for anterior communicating aneurysm (ACoA) patients has significantly reduced the mortality and disability rate. Some patients with ACoA achieved clinical recovery after the operation but suffered from "ACoA Syndrome," manifested in cognitive functions such as memory, attention, and language [1,2]. Deficits in cognitive abilities, such as language fluency, orientation, executive function, and personality changes associated with frontal lobe damage, are frequently reported in the neuropsychological evaluation of patients after ACoA aneurysm temporary clipping [3]. Temporary clipping of the A1 segment is essential during complex microsurgical clipping, thus minimizing the risk of premature rupture and providing a more accessible and safer dissection during aneurysm surgery [4,5]. Studies have shown that patients with a temporary clipping duration longer than 9 minutes are more likely to develop cognitive impairment evaluated by Wisconsin Card Sorting Test (WCST) [4]. Evaluation of the risk of short-term and long-term cognitive deficits associated with temporary vessel occlusion would provide a better understanding of the contributions of subarachnoid hemorrhage (SAH). In addition, determining the occurrence of cognitive impairment resulting from the temporary clipping may provide adequate counseling on the risks and benefits of temporary vessel occlusion.

Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) are cognitive screening scales for cerebrovascular diseases, but their effect on assessing cognitive dysfunction after temporary clipping is unclear [3,6]. MMSE is a widely used scale for cognitive impairment, and the subjects answered the questionnaire including five items related to orientation, registration, attention and calculation, recall, and language and praxis. The standard score was 27-30 points, and those with less than 27 points were considered to have cognitive dysfunction [6]. The MoCA scale involves seven parts: visuospatial & Executive function, Naming, Attention, Language, Abstraction, Delayed recall, and Orientation, and the total score is 30 points. The scale has good parallelism with MMSE [3]. The simultaneous application of the above scales will comprehensively evaluate the cognitive impairment of patients. This study aimed to explore the effects of temporary clipping duration on frontal lobe functions in patients operated for ruptured ACoA aneurysm. The patient's cognitive function was evaluated at 6-month and 12-month post-surgery. We conducted MMSE and MoCA evaluation in each phase. The neurological scores were compared between each group and two phases. We speculated that patients with short occlusion time will achieve better cognitive recovery and two scales could be used in cognitive impairment evaluation after temporary clipping in ACoA surgery.

Methods

Characteristics of participants

Forty-five patients with ACoA admitted to the hospital from May 2014 to May 2020 were collected in this case-control study. All institutional and national guidelines for the care of humans were followed. All research data has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The Ethics Committee has approved the project. There were 23 males and 22 females, ranging from 29 to 72 years (mean age 47.53±11.17 years). The above 45 patients with ACoA were confirmed by total cerebral angiography or CT angiography before surgery. Twenty-one cases were classified as Hunt-Hess Grade 1, and 25 cases were classified as Hunt-Hess Grade 2. Fisher subarachnoid hemorrhage CT grading classifies Grade 2 in 19 cases and Grade 3 in 25 cases. According to the temporary clipping time, patients were classified in Group B with occlusion time shorter than nine minutes, whereas Group C with occlusion time equal to or longer than nine minutes. Besides, 24 volunteers (Group A) with no previous history of mental illness were recruited as the volunteer group, including 13 males and 11 females aged 29 to 69 years (mean age 47.50±12.30 years).

Table1: Clinical characteristic of subjects ($\overline{X} \pm s$).

	Group A (n=24)	Group B (n=21)	Group C (n=24)	*P* value
female, *n*(%)	11 (45.83%)	10 (47.62%)	12 (50.00%)	0.9589
age	47.50±12.30	49.76±10.16	45.58±11.85	0.4831
Smoke Status, *n*(%)	14 (58.33%)	10 (47.62%)	14 (58.33%)	0.7126
Trevious smoker	7 (29.17%)	4 (19.04%)	8 (33.33%)	0.5503
Current smoker	7 (29.17%)	6 (28.57%)	6 (25.00%)	0.9415
Never smoker	10 (41.67%)	11 (52.38%)	10 (41.67%)	0.7126
Current Alcohol Use (>=2-3time/ week) *n*(%)	16 (66.67%)	15 (71.42%)	17 (70.83%)	0.9287
Current Caffeine Use(>=2-3time/ week) *n*(%)	14 (58.33%)	12 (52.38%)	14 (58.33%)	0.9958
Hypertension	10 (41.67%)	11(52.38%)	12 (50.00%)	0.7464
Education Years Range Median (IQR)	12 (10-16)	11(9.5-13)	12(10-15)	0.1421
Hunt-Hess Grade		Grade 1 (9) Grade 2 (12)	Grade 1 (11) Grade 2 (13)	>0.9999
Fisher		Grade 2 (9) Grade 3 (12)	Grade 2 (10) Grade 3 (14)	>0.9999

All the included patients were confirmed to be anterior communication aneurysms by total cerebral angiography or CT angiography before surgery, and the following conditions were excluded: history of Alzheimer's disease, previous history of mental or psychiatric disorders, Hunt-Hess grade 0, 3, 4, or 5, multiple intracranial or other sites aneurysms, history of intracranial lesions, and craniotomy. This clinical trial also considered hypertension as a possible factor affecting cognitive function. The subjects in this study did not have hypertension or were controlled within the normal range by medication. We also considered the effects of nicotine, alcohol, and caffeine on cognitive function. All patients and volunteers underwent detailed intake histories of nicotine, alcohol, and caffeine (including tea, coffee, and other caffeine drinks). Patients and volunteers were not addicted to nicotine, alcohol, or caffeine and were instructed to control smoking, alcohol, and caffeine intake. Considering that cognitive impairment is age-related and education-related, we standardized the age distribution of patients and volunteers at enrollment. There was no significant difference in the composition of age and education level between the volunteer group and the aneurysm group. The clinical characteristics of the subjects are shown in Table 1.

Characteristics of neurosurgery

Temporary clipping surgery was performed through a left lateral supraorbital approach in 13 patients in Group B and 11 patients in Group C, whereas a right lateral supraorbital approach in the remaining patients. All patients were invariably treated surgically through a standard lateral supraorbital craniotomy and microsurgical clipping after SAH. The patients were kept under normothermia and normotension. The location of temporary clipping and occlusion time was recorded. After surgery, standard medical management was used, including calcium antagonists, volume expansion, hemodilution, and optimal general hemodynamic and medical status maintenance. CT scans were obtained from the patients on the first day, second day, first month, the sixth month, and the twelfth month additionally in the case of clinical needs. Radiological and clinical ischemic findings were recorded.

Neuropsychological assessment

The neuropsychological study was conducted in two phases. The first neuropsychological evaluation was administered about six months after surgery. Additionally, a second neuropsychological test at about 12 months after surgery was administered in all patients of groups A, B, and C. MMSE and MoCA were conducted by two experienced doctors who carried out each experiment. All patients were individually tested during a single session. The examination arrangement was the same for the patients in the control group. The participants' scores were adjusted for the effects of education level and age on the results [3,6].

Statistical analysis

GraphPad Prism 7(GraphPad Software, San Diego, USA) was used to analyze the data of each group. Measurement data were expressed as average± standard deviation (± SD). Data sets in each group were tested for normality via Kolmogorov-Smirnov tests. Nonparametric Kruskal-Wallis tests were conducted when data did not fit the Gaussian distribution among the three groups. Nonparametric Wilcoxon test were conducted between two groups. A two-tailed Spearman correlation analyzed the correlation between blocking time and MMSE and MoCA scores. $P < 0.05$ was considered statistically different and $P < 0.01$ was considered significantly different.

Results

Evaluation of participants

Male/female ratio, age, Hunt–Hess grade at surgery, and Fisher CT grade at admission were similar in Group B and C and Group A, if applicable (Table 1). All patients were operated on between the first and the third day after SAH. In group B, temporary clipping was applied for 21 ACoA aneurysms. The mean duration of occlusion time for both A1 was 7.98±0.80 min (6.7–8.9 min). In group C, temporary clipping was applied for 24 ACoA aneurysms. The mean duration of occlusion time for both A1 was 11.41±2.11 min (9–15.3 min). No clinical or radiographic strokes, secondary to temporary clipping, were detected in any patients of group B and C. There were no statistically significant differences between patient groups and the control group for age, sex and education level distribution ($P > 0.05$). Table 1 shows the detailed data of the patients and controls.

MMSE assessment revealed cognitive dysfunction in AcoA patients after temporary clipping.

In the first administration of the MMSE, at about six months after surgery, there was a statistically significant difference between Group A and Group C on orientation ($P < 0.01$), attention and calculation ($P < 0.05$), recall ($P < 0.01$), and language ($P < 0.05$). As for Group B, orientation ($P < 0.01$), attention and calculation ($P < 0.05$) items showed statistical reduction compared with Group A. There are no significant differences between Group B and Group C ($P > 0.05$) in the first administration. In the second administration, at about 12 months after surgery, there was a statistically significant difference between Group A and Group C in orientation ($P < 0.01$), attention and calculation ($P < 0.05$), recall ($P < 0.01$), and language ($P < 0.01$). As for Group B, the orientation ($P < 0.01$) item showed a statistical reduction compared with Group A. Besides, the orientation item showed significant differences between Group B and Group C ($P < 0.01$). The total scores were summed up for further evaluation. The results showed that compared with Group A, Group B and C showed a statistical reduction in total scores ($P < 0.01$). There are significant differences between Group B and Group C ($P < 0.05$). In the first phase, postoperative cognitive dysfunction occurred in 23 patients (51.11%) whose total MMSE scores were less than 27. In Group B, whose occlusion time is shorter than 9 minutes, the cognitive dysfunction ratio is 28.57%, whereas 70.83% in Group C. In the second phase, MMSE total scores less than 27 points were detected in 22 patients (48.89%). In Group B, whose occlusion time is shorter than 9 minutes, the cognitive dysfunction ratio is 19.05%, whereas 75.00% in Group C. Detailed results were shown in Table 2.

Table 2: MMSE test results ($\bar{x}$ ± s).

First Phase	Group A (n=24)	Group B (n=21)	Group C (n=24)
Total scores	28.75±0.68	26.29±1.71**	24.33±1.97**
Orientation	9.71±0.55	8.48±1.03**	7.58±1.10**
Registration	2.75±0.44	2.57±0.60	2.29±0.81
Attention and Calculation	4.71±0.55	4.14±0.65**	4.21±0.66*
Recall	2.88±0.34	2.48±0.68	2.33±0.70**
Language and Praxis	8.71±0.46	8.62±0.59	7.92±1.25*
Second Phase	**Group A (n=24)**	**Group B (n=21)**	**Group C (n=24)**
Total scores	29.00±0.72	27.00±0.94**	24.91±1.59**$
Orientation	9.79±0.41	8.67±0.91**	7.71±1.00**$
Registration	2.75±0.44	2.66±0.48	2.42±0.72
Attention and Calculation	4.71±0.55	4.33±0.65	4.25±0.61*
Recall	2.91±0.28	2.66±0.48	2.38±0.65**
Language and Praxis	8.83±0.48	8.66±0.48	8.16±1.58**

Note: Compared with Group A (control group), **P<0.05, **P<0.01;* Compared with Group B (aneurysm group< 9 min group), *$P<0.05, $$P<0.01.*

MoCA assessment revealed cognitive dysfunction in AcoA patients after temporary clipping:

This study also uses MoCA scales to assess cognitive dysfunction after temporary clipping. At about 6 months after surgery, there was a statistically significant difference between Group A and Group C on visuospatial & executive function (P < 0.01), naming (P < 0.01), attention (P < 0.01), delayed recall (P < 0.01) , and orientation (P < 0.01). As for Group B, orientation (P < 0.01), attention (P < 0.05) items showed statistical reduction compared with Group A. There are significant differences between Group B and Group C on visuospatial & executive function (P < 0.01), naming (P < 0.01), and attention (P < 0.01) in the first administration. At about 12 months after surgery, there was still a statistically significant difference between Group A and Group C on the same items in the second administration. As for Group B, the orientation (P < 0.01) item showed a statistical reduction compared with Group A. Visuospatial & executive function, naming, and attention showed significant differences between Group B and Group C (P < 0.01). The total scores were summed up for further evaluation. In the first administration, the results showed that compared with Group A, Group B (P < 0.05) and C (P < 0.01) showed a statistical reduction. There are significant differences in total scores between Group B and Group C (P < 0.05). In the first administration, the results showed that Group C (P < 0.01) showed a statistical reduction compared with Group A. There are significant differences in total scores between Group B and Group C (P < 0.05). However, there are no statistical differences in total scores between Group A and Group B (P > 0.05). Detailed results were shown in Table 3.

Table 3: MoCA test results (±s).

First Phase	Group A (n=24)	Group B (n=21)	Group C (n=24)
MoCA total score	26.46±1.29	24.05±2.06*	19.42±1.67**$$
Visuospatial & Executive function	4.50±0.51	4.43±0.81	3.25±0.53**$$
Naming	2.58±0.56	2.67±0.48	1.71±0.46**$$
Attention	5.54±0.51	5.19±0.60*	3.91±0.65**$$
Language	2.42±0.50	2.43±0.60	1.96±0.55
Abstraction	1.71±0.46	1.76±0.44	1.42±0.50
Delayed recall	4.29±0.55	3.81±0.87	3.13±0.90**
Orientation	5.42±0.50	3.76±0.54**	4.04±0.62**
Second Phase	**Group A (n=24)**	**Group B (n=21)**	**Group C (n=24)**
MoCA total score	26.58±1.25	25.38±1.28	21.04±1.85**$$
Visuospatial & Executive function	4.50±0.51	4.67±0.66	3.45±0.51**$$

Naming	2.58±0.50	2.86±0.36	2.08±0.65*$$
Attention	5.54±0.51	5.38±0.49	4.13±0.74**$$
Language	2.41±0.50	2.71±0.46	2.13±0.45$$
Abstraction	1.75±0.44	1.81±0.40	1.58±0.50
Delayed recall	4.33±0.48	4.00±0.84	3.42±0.83**
Orientation	5.45±0.51	3.95±0.67**	4.25±0.74**

Note: Compared with Group A (control group), **P<0.05, **P<0.01;* Compared with Group B (aneurysm group< 9 min group), *$P<0.05, $$P<0.01.*

MMSE and MoCA total scores comparison in the first and second phase

We conducted paired Wilcoxon test to reveal cognitive improvement in the first and second phases. The result revealed that in Group A, the volunteer showed no significant differences in the first and second phases in both MMSE and MoCA evaluation. In the MMSE and MoCA evaluation of group B, there is a significant improvement in the second evaluation compared with the first evaluation (P < 0.01). As for MoCA evaluation of Group C, there is a statistical improvement in the second evaluation compared with the first evaluation. But there are no statistical differences in total scores comparison in Group B MMSE evaluation (P > 0.05) (Figures 1A & 1B).

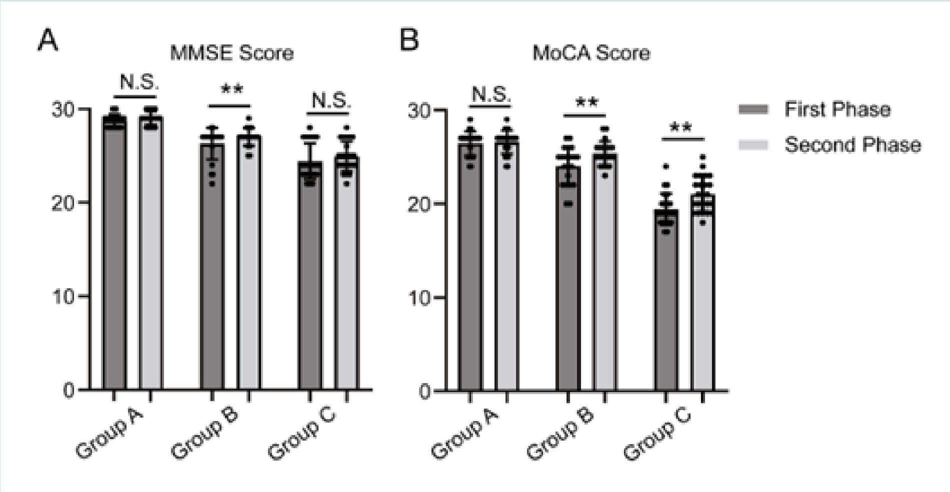

Figure 1A: First and second phase comparison of MMSE total scores. There was a significant difference between Group B, but no significant differences between Group A and Group C were observed between the first and second evaluations.
Figure 1B: First and second phase comparison of MoCA total scores. There was a significant difference between Group B and Group C, but no significant differences between group A were observed between first and second evaluations.

Discussion

The anterior communicating artery is anatomically deep and has structural variations. In addition, due to the many perforating blood vessels in the A1 segment of the anterior artery, a ruptured aneurysm may cause SAH, the formation of a hematoma at the base of the skull and frontal lobe and leading to vasospasm [7]. SAH after ruptured ACoA may cause postoperative cognitive impairment. Although physical brain damage is relatively rare, it has been reported that up to 50% of patients remain with cognitive impairment [8]. Studies have shown that gender, education level, and the Hunt-Hess grade are all critical factors affecting the prognosis of patients [9-11]. The ruptured aneurysm can cause metabolic disorders and harmful product accumulation. It can also lead to hemodynamic changes, vascular permeability changes, blood-brain barrier damage, and self-regulation of peripheral vascular diseases [11]. Extensive ischemic and hypoxic injury of brain tissue caused by blood circulation disturbance after SAH exacerbates these changes [10]. It has been reported that the Fisher CT grading can evaluate the cognitive status of patients after surgery [12]. In this study, the Fisher CT grading revealed Grade 2 in 19 cases and Grade 3 in 26 cases. The higher the grade, the worse the cognitive evaluation of the patients' executive and memory ability (Data not shown). A multicenter retrospective study of multivariate Cox regression showed that the female patients and longer loss of consciousness at the onset of SAH were independently associated with cognitive impairment [9]. The vasospasm caused by hematoma after SAH can lead to frontal lobe cortex ischemic injury, causing traffic artery and perforator area infarction and hemorrhage. It would further lead to cerebral edema and increased intracranial pressure [6,12]. MMSE and MoCA are classic neurological dysfunction evaluation scales. As far as we know, it is the first time that it has been used to evaluate the temporary clipping effect on neurological dysfunction in ACoA surgery. We set the patient group according to the temporary occlusion time in this study.

For patients with a temporary blocking duration of fewer than 9 minutes, MMSE and MoCA showed that the neurological function had improved between the first and second phase evaluation, indicating that the impairment of neurological dysfunction was temporary. As for the patients with a temporary blocking duration equal to or longer than 9 minutes, MMSE showed no significant improvement between two evaluations, while MoCA showed a significant improvement, indicating that MoCA was more sensitive in the evaluation. The test results showed statistical differences mainly in orientation, attention, recall, and executive function between the patients and the volunteer group 6-month and 12-month after surgery. Orientation reflects the patients' cognition of the current time and space dimensions [5,13,14]. Both attention and recall functions depend on the prefrontal lobe [15,16]. Executive function is a complex, advanced function that involves planning, logic, attention, and execution [5,17]. The frontal lobe, angular gyrus, middle temporal gyrus, and bilateral parietal lobes were involved in execution [17]. These results partially indicated a correlation between occlusion time and cognitive dysfunction related to frontal lobe damage. In addition, a recent study showed that ischemia and hypoxia lead to gyrus change in MRI [18].

Therefore, MRI imaging data will further increase our understanding of changes in brain regions after temporary occlusion. During the operation, temporary occlusion of the A1 segment and separation of perforating vessels made the ACoA aneurysm clipping operation more likely to cause postoperative vessel injuries and ischemia [19,20]. Due to the morphology of the aneurysm, temporary occlusion of the dominant A1 segment is usually essential in the aneurysm and arachnoid separation to prevent aneurysm rupture [7]. Akyuz found that operating clipping of anterior communicating ruptured aneurysm, limiting temporary A1 blocking time within 8.2±2.9 minutes, was no clinical or radiographic ischemic brain injury. However, when the temporary blocking time was more than 9 min, patients can be diagnosed with resistant cognitive impairment during long-term follow-up WCST [4]. In addition, when unilateral temporary occlusion of segment A1 occurs, the oxygen concentration in the surgical frontal lobe can decrease by more than 20%, thereby exacerbating ischemic injury [21]. Our study has limitations. Further follow-up assessment of patients and volunteers will clarify the relationship between the duration of intraoperative temporary blocking and cognitive improvement. In addition, the sample size was small. Expanding the sample size and multicenter cooperation would be conducive to drawing more accurate conclusions to determine the specific reference occlusion time during surgery.

Conclusion

Our study shows that the MMSE and MoCA could be used in cognitive impairment evaluation after temporary clipping in ACoA surgery. Cognitive dysfunction showed significant improvement when the temporary occlusion time was less than 9 minutes. Therefore, surgeons should shorten temporary clipping time in clinical practice, which greatly improves patients' prognostic cognitive function.

Disclosure and conflicts of interest

This work was supported by the National Natural Science Foundation of China [grant number 81971171].

Compliance with ethics guidelines. The study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Conflict of Interest

Jing Wang, Zongqi Wang, Yu Wu, Xue Sun, and Xiaoou Sun declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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DOI: 10.32474/SJPBS.2023.07.000255