COGNITIVE OUTCOMES ON STENTING WITH MEDICAL TREATMENT VESUS MEDICAL TREATMENT ALONE FOR SYMPTOMATIC MIDDLE CEREBRAL ARTERY STENOSIS COMPANIED WITH COGNITIVE IMPAIRMENT

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ABSTRACT

Objective: *The effects of intensive drug therapy and stenting combined drug therapy on cognitive function in patients with symptomatic middle cerebral artery stenosis accompanied by cognitive impairment were compared during follow-up periods of 1 month and 6 months.*

Methods: *A single-centre retrospective cohort study was conducted in 77 patients with symptomatic middle cerebral artery stenosis accompanied by cognitive impairment. Patients were divided into an intensive drug treatment group and a stenting combined drug treatment group. The MoCA scores before the two treatments, at one month of follow-up and at six months of follow-up were compared, and subgroup analysis of different perfusion states before stenting combined with drug therapy was carried out.*

Results: *In the stenting combined drug treatment group, the total MoCA score, language repetition and delayed recall score were higher than those scores in the intensive drug treatment group at one month and six months of follow-up (P<0.05), and the attention score was also improved at six months follow-up. There was no change in the total MoCA score in the intensive drug treatment group compared with the baseline during the follow-up period, but the total MoCA score, clock drawing test, attention and delayed recall in the stenting combined with drug treatment group showed benefits compared to those in the baseline at the one month follow-up (P<0.05). During the one-month follow-up period, the normal perfusion group could only benefit from delayed recall (1.11±0.963 VS 1.61±1.037, P<0.05). The abnormal perfusion group benefited from the total MoCA score, clock drawing experiment, attention, delayed recall and orientation. After six months follow-up, the total MoCA score in the abnormal perfusion group was more beneficial than that in normal perfusion group (3.875 vs 1.222, P<0.05).*

Conclusion: *For patients with symptomatic middle cerebral artery stenosis with cognitive impairment, stenting combined with drug therapy can improve cognitive impairment, but intensive drug therapy cannot benefit from cognitive function.*

Keywords: *Symptomatic middle cerebral artery stenosis companied with cognitive impairment, stenting combined with drug therapy, cognitive function.*

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Introduction

Intracranial atherosclerotic stenosis is a critical cause of ischemic stroke, accounting for nearly 40% of all ischemic stroke events in the Asian population[1, 2]. In recent years, there has been increased focus on the relationship between intracranial atherosclerotic stenosis and cognitive dysfunction. Intracranial atherosclerotic stenosis is considered to be a risk factor for cognitive impairment[3], which is related to mild cognitive impairment and dementia and plays an important role in the pathological progression of mild cognitive impairment to dementia[4, 5]. Ischemic stroke events and cerebral blood flow hypoperfusion are important factors in cognitive impairment caused by symptomatic intracranial artery stenosis[3, 6]. At present, treatments for symptomatic intracranial atherosclerotic stenosis include endovascular therapy and drug therapy. Although intravascular therapy can effectively improve cerebral blood

flow hypoperfusion[7], the incidence of ischemic events during postoperative follow-up is significantly higher than events occurring in drug therapy. Intensive drug therapy can reduce recurrent stroke[8, 9], but there is still little relevant research on whether it can improve the hypoperfusion state of brain tissue. Therefore, it is not clear whether the two treatments will provide cognitive function benefits.

The current study focused on treating carotid stenosis. A number of studies investigating carotid stenting found that it can improve cognitive function by reducing the incidence of stroke and improving the perfusion status of brain tissue; moreover, the effect is superior to single drug therapy alone[10-12].

The SAMMPRIS study evaluated cognitive impairment as a secondary end point and found that the stenting treatment group was not superior to the intensive drug treatment group in improving cognitive function[13]. However, because of the high incidence of postoperative ischemic stroke complications in the stenting treatment group in this study, some of the two groups of patients who did not have any stroke events during the follow-up period were selectively evaluated. In addition, subgroup analysis was not conducted based on different preoperative perfusion status, which had some limitations.

The middle cerebral artery is an important intracranial liability blood vessel in an ischemic stroke event, and atherosclerotic stenosis has been linked to cognitive dysfunction[14]. Patients may show varying degrees of impairment in a variety of cognitive domains, such as language, memory, attention, visual space and executive function[6].

A retrospective cohort study was conducted in patients with symptomatic M1 segment severe stenosis of the middle cerebral artery with cognitive impairment to evaluate whether the two treatments (intensive drug therapy and stenting combined with drug therapy) produced cognitive benefits and the difference between the two treatments. Additionally, post-operative cognitive function was analysed based on the different brain tissue perfusion status of the stenting treatment group.

Materials and methods

Screening of research cases

With the consent of the hospital ethics committee, all patients provided full informed consent and voluntarily chose intensive drug therapy or stenting combined with drug treatment. A total of 155 hospitalized patients with symptomatic middle cerebral artery stenosis from September 2016 to March 2019 in the Department of Neurointervention of the Hospital of Qingdao University were analysed retrospectively. Among these, 63 patients were treated with intensive drugs and 92 patients were treated with stenting combined with drug treatment, according to the following criteria for screening.

Inclusion criteria:

• The patients' age was between 45 years old to 75 years old;

•The patients had symptomatic middle cerebral artery stenosis with TIA or stroke within 90 days and were taking at least one antithrombotic drug;

• The most recent ischemic stroke occurred more than two weeks ago;

• Cerebral angiography (DSA) confirmed that the responsible site was the M1 segment of middle cerebral artery;

• The warfarin-aspirin symptomatic intracranial disease (WASID) method identified the degree of stenosis at 70% to 99%;

• Etiological classification of TOAST is the large artery atherosclerosis type;

• The Montreal cognitive scale (MoCA) score was less than 26 points;

• Preoperative CT perfusion imaging (CTP) was used to evaluate the perfusion status of the brain tissue in patients treated with stenting combined with drug treatment.

Exclusion criteria:

• In addition to the responsible vessels, there were intracranial, extracranial or macrovascular stenosis equal to or greater than 50% or occlusion;

• The patients had a history of central nervous system diseases such as head trauma, epilepsy, Parkinson's disease and Alzheimer's disease;

• There was previous history of intracranial haemorrhage, cerebral arteriovenous malformations and cerebral venous sinus thrombosis;

• The patients had a history of past mental illness and dependence on psychotropic drugs. Patients with severe cardiac insufficiency (NYHA grade: III grade, IV grade), obstructive sleep apnoea and so on affected cognitive function evaluation. Brain MRI showed white matter high signal Fazekas grade 3:

• The Hachiski ischemia scale suggested that cognitive dysfunction may be caused by non-vascular factors. The Hamilton depression scale score was less than 8 points.

Through the above screening methods, a total of 12 cases were found to have incomplete data,

including three cases with anaphylaxis history of iodine contrast agent that were unable to complete CTP and DSA, one case unable to complete craniocerebral MRI and CTP due to ankylosing spondylitis, two cases that refused to conduct DSA, three cases that failed to complete the evaluation of MoCA scale or Hamilton depression scale and unknown causes of uncompleted craniocerebral MRI or CTP in three cases. Therefore, a total of 136 patients completed the evaluation of craniocerebral MRI, CTP, DSA, MoCA scale, Hamilton depression scale and Hachiski ischemic scale during hospitalization. According to the inclusion and exclusion criteria, a total of 77 cases met the criteria: 35 cases in intensive drug treatment group and 42 cases in stenting combined with drug treatment group.

Management scheme

Intensive drug treatment group:

• All patients were treated with aspirin 100mg qd combined with clopidogrel 75mg qd antithrombus therapy after admission;

• The patients continue to use the above dual antiplatelet therapy regimen for 90 days after discharge, and aspirin or clopidogrel should be used for antiplatelet therapy in a sequential and long-term manner.

Management of key risk factors:

• The target value of systolic blood pressure was less than 140 mmHg (if the patients combined with diabetes, the target value is less than 130 mmHg);

• The target value of low-density lipoprotein was less than 1.8 mmol/ L (70 mg/dl) or at least a 50% reduction;

• The glycosylated haemoglobin was less than 7%;

• Patients were encouraged to give up smoking;

• Patients were encouraged to carry out aerobic exercise 30 minutes each time, 2 to 3 times a week[15].

Stenting combined with drug treatment group

The choice of local anaesthesia or general anaesthesia was determined by the operator according to the clinical situation of the patient. A 6F or larger arterial sheath and guide catheter were inserted through the thigh artery. Heparin was used to ensure that the activation coagulation time was 150 s to 200 s, and the guide catheter was placed in the C1 or C2 segment of the internal carotid artery.

The stenosis site and stenosis degree were determined by radiography. The wingspan self-expanding stent (Boston Scientific, USA) or Apollo balloon dilated stent (MicroPort NeuroTech, Shanghai, China) were selected by the operator according to the surgical vascular path and lesion typing (Mori typing)[16]. Before releasing the self-expanding stent, the appropriate size (the named pressed balloon diameter was 60% to 80% of the normal lumen diameter) of the Gateway balloon (Boston Scientific, USA) was selected for pre-dilatation. Before releasing the balloon dilated stent, the appropriate size (the named pressed balloon diameter was 50% of the normal lumen diameter) of the MINITREK balloon (Abbot Vascular, USA) or Gateway balloon (Boston Scientific, USA) may be selected for pre-dilatation.

The completion time of each pre-expansion operation mentioned above is equal to or greater than 40 s. The balloon expansion stent selection size is 85% to 95% of normal lumen diameter. Tirofiban was used in patients with acute stent thrombosis during operation with 20ug/kg intravenous infusion and 0.4ug/(kg·min) intravenous pumping for 24 hours.

Perioperative management: It takes equal to or more than five days for patients to take aspirin 100mg qd combined with plavix 75mg qd antithrombus therapy before operation. If the medical treatment was equal to or less than five days, patients were temporarily given a load dose of 300mg plavix 12h to 24h before the operation.

Intracranial haemorrhage was excluded with routine re-examination of craniocerebral CT after operation. The patient's hyperperfusion syndrome and risk of bleeding was assessed by the surgeon, and an individualized management scheme was developed. After the operation, the systolic blood pressure (SBP) was controlled at 100 to 130mmHg, or the diastolic blood pressure (DBP) was maintained at less than 90mmHg by using intravenous or oral antihypertensive drugs.

Based on body weight, low molecular weight heparin (LMWH) was injected subcutaneously every 12 hours after operation for three days, and patients at high risk of bleeding had bleeding properly reduced or stopped. The antithrombus and main factors management scheme after discharge were the same as those in the intensive drug treatment group.

Monitoring and management of antiplatelet drug resistance: All patients in both groups were evaluated for clopidogrel resistance with thrombelastogram or clopidogrel-related gene monitoring.

If clopidogrel resistance was present, ticagrelor 90mg bid was preferred instead, and cilostazol 50mg bid was selected for the same time as clopidogrel if there was drug intolerance to clopidogrel.

CTP examination

All patients in the stenting combined with drug treatment group were examined with CT perfusion imaging (CTP) at admission with DISCOVERY CT750 HD gemstone CT (GE company, USA). The image was read by two experienced neuroimaging physicians. According to the anatomical relationship of the cerebral artery blood supply, the symmetrical region of interest (ROI) was selected in the bilateral middle cerebral artery to clearly display the bilateral MCA M1 segment as the starting plane. Four cross-sections were selected, and the following cerebral perfusion values were obtained with CT Perfusion software: regional cerebral flow (CBF), regional cerebral volume (CBV), mean transit time (MTT), time to peak (TTP). The average values of each parameter were taken to compare the lesion side and the healthy side.

According to these indexes, the cases in the stenting combined drug treatment group were divided into the normal perfusion group and the abnormal perfusion group. There was no difference in the above four indexes between the lesion side and the healthy side in the normal perfusion group.

The abnormal perfusion group was defined as the following: cerebral circulation reserve compensation period: normal or prolonged MTT, prolonged TTP, normal or mild decrease in rCBF, normal or elevated rCBV; cerebral circulation reserve decompensation period: prolonged TTP, MTT, decreased rCBF, normal or decreased rCBV. If one of these two criteria were met, the patient was classified in the abnormal perfusion group.

Follow-up

Cognitive function was evaluated by a professional neuropsychologist using the MoCA scale[17], which can evaluate visual space, execution function, naming, memory, attention, language ability, abstract thinking, delayed recall, orientation and other cognitive domains. The full score of the MoCA scale is 30 points, and a score equal to or greater than 26 points was regarded as indicating normal cognitive function. A lower score indicated the degree of severity of the cognitive impairment. If the number of years of education were equal to or less than 12 years, one point was be added. The time points of cognitive function evaluation included hospitalization, one month follow-up after discharge, six month follow-up after discharge or hospitalization follow-up. Additionally, ischemic events (stroke and TIA) were recorded during one month follow-up.

Statistical analysis

Analysis of endpoint events

• The inpatient baseline, the total MoCA scores at one month and six months after discharge from the intensive drug treatment group and stenting combined with drug treatment group, and the differences within and between each individual score group were evaluated;

• The inpatient baselines of preoperative normal perfusion and abnormal perfusion patients in the stenting combined with drug treatment group as well as the total MoCA score at one month and six months after discharge and the difference within and between each individual score group were evaluated;

• The incidence of adverse events (including transient ischemic attack, ischemic stroke, symptomatic intracranial haemorrhage and death) in the two groups during the follow-up periods were evaluated;

• The measurement data in clinical characteristic of the patient were expressed as mean ± standard deviation (x±s).

To determine whether there was a statistical difference between the two groups, a t-test was applied if the data had a normal distribution; a rank sum test was used to analyse data that were not normally distributed. The counting data were expressed as frequency and percentage, and a chi-square test was used to determine whether there was statistical difference between the two groups.

To compare the MoCA scores, repeated measurement variance analysis was used to evaluate the interaction between time and treatment and statistical differences in scores at each time point between groups and within groups.

$P<0.05$ indicated that the difference was statistically significant. All statistical data were analysed with SPSS23.0 system.

Results

Clinical characteristics of patient baseline features

A total of 77 patients were enrolled in this study, of which 35 patients were in the intensive drug treatment group, and 42 patients were in the stenting combined with drug treatment group.

There were no statistical differences in age, sex, years of education, dextromanuality, diabetes, hypertension, hypercholesterol, smoking history, NIHSS score, type of ischemic events caused by responsible blood vessels, lesion location and responsible vascular stenosis rate ($P>0.05$).

Clinical features	Drug treatment group (N=35)	Drug combined with stenting treatment (N=42)	P
Average age (years old)	64.06±8.36	62.67±8.544	0.475
Male	19 (54.3%)	22 (52.4%)	0.868
Years of education	7.89±3.924	9.36±3.641	0.072
Dextromanuality	35 (100.00%)	41 (97.6%)	1.000
Diabetes mellitus	9 (25.7%)	15 (35.7%)	0.346
Hypertension	25 (71.4%)	32 (76.2%)	0.635
Hypercholesterolemia	18 (51.4%)	23 (54.8%)	0.770
Smoking history	14 (40.0%)	17 (40.5%)	0.966
Ischemic events			
TIA	16 (45.7%)	15 (35.7%)	0.373
Stroke	19 (54.3%)	27 (64.3%)	
Admission NIHSS score	1.43±1.74	1.76±1.845	0.417
Site of lesion			
LMCA	21 (60.0%)	22 (52.4%)	0.503
RMCA	14 (40.0%)	20 (47.6%)	
Responsible artery stenosis rate (%)	82.94±8.87	85.98±9.33	0.150

Table 1: Basic clinical features of the included patients. TIA: transient ischemic attack NIHSS: National Institute of Health stroke scale. LMCA: Left Middle Cerebral Artery. RMCA: Right Middle Cerebral Artery.

Perioperative stenting combined with drug treatment group during hospitalization

In the stenting combined with drug treatment group, the average rate of responsible vascular stenosis was 85.58±9.32, and the average residual stenosis rate was 14.83±7.454. Complications related to the operation occurred in two cases (4.8%) during hospitalization, and one case had stent thrombosis leading to stent occlusion of the left middle cerebral artery on the second day after surgery. Balloon angioplasty at the stent of the left middle cerebral artery was performed in emergency, and the occlusive vessels were successfully opened. Intravenous administration of tirofiban sequential oral antiplatelet drugs (aspirin 100mg qd + ticagrelor 90mg bid) was carried out for treatment. At discharge, craniocerebral MRI showed cerebral infarction in the left basal ganglia, left temporal and parietal cortex, and the NIHSS score increased from 2 points before operation to four points. One case with craniocerebral MRI showed cerebral infarction in the right basal ganglia; the muscle strength of the left limb decreased from grade 5 to grade 4, and the NIHSS score increased from 0 points before operation to 2 points.

Cumulative occurrence of adverse events in the two groups during the follow-up period

During the one-month follow-up period, two cases (4.8%) of the total adverse events occurred in the stenting combined with drug treatment group, and four cases (11.4%) in the intensive drug treatment group. The cumulative adverse events that occurred during the six-month follow-up period included three cases (7.1%) vs six cases (17.1%).

In the intensive drug treatment group, two cases of TIA and two cases of ischemic stroke occurred during the one-month follow-up period after discharge. Two cases of ischemic stroke occurred during the follow-up period from one month to six months. Ischemic stroke in the four patients was confirmed by CTA or DSA, determining that stroke events were caused by responsible blood vessels at the time of admission, and one patient chose intracranial artery stent implantation at 7 months of follow-up. No symptomatic intracranial haemorrhage or death occurred.

No adverse events occurred in the stenting treatment group during the one-month follow-up period. One case of symptomatic ischemic event occurred during the follow-up period of one month to six months. The NIHSS score of the patient increased from 0 points before the operation to 5 points at the time of follow-up. A DSA examination was performed in hospital and showed restenosis of the left middle cerebral artery stent, and the stenosis rate was 90%. Balloon dilatation was performed to resolve the restenosis lesion. No death occurred.

Comparison of the total MoCA score and cognitive domain score at different time points

The total MoCA scores of the two groups in different treatment methods and different time points are shown in Table 2. There was no significant difference in overall comparison between the two groups ($F=3.319$, $P=0.072$), but there was a significant difference between different follow-up time points ($F=15.491$, $P<0.001$). As shown in Figure 1, there was an interaction between different treatment methods and time points ($F = 20.904$, $P<0.001$).

Comparison of the total MoCA scores at different time points in the same treatment method revealed no statistically significant differences in the intensive drug treatment group scores at different time points ($P<0.05$). In the stenting combined with drug treatment group, the follow-up for one month was 1.762 higher than the hospitalization baseline (95% confidence interval: 1.060, 2.464, $P<0.001$),

the follow-up for 6 months was 0.976±0.198 higher than the one-month follow-up (95% confidence interval: 0.493, 1.460, P<0.001), and the follow-up for 6 months was 2.738±0.326 higher than the hospitalization baseline (95% confidence interval: 1.943, 3.533, P<0.001). Comparison of the total MoCA score between the two groups at the same time point showed no statistical difference in the hospitalization baseline level between the two groups (P = 0.588). At one month of follow-up, the stenting combined with drug treatment group was 2.162 higher than the intensive drug treatment group (95% confidence interval: 0.425, 3.899, P≤0.015).

At six months of follow-up, the stenting combined with drug treatment group was 2.738 higher than the intensive drug treatment group (95% confidence interval: 1.148, 4.328, P = 0. 001).

MoCA score	Drug treatment group (N=35)			Stenting combined with drug treatment group (N=42)		
	Before drug treatment	After 1 month	After 6 months	Before operation	1 month after operation	6 months after operation
Total score	18.20±3.72	17.46±4.104	17.86±3.474	17.86±4.292	19.62±3.547$^{\#\&}$	20.60±3.500$^{\#\&*}$
Alternating connection	0.40±0.497	0.34±0.482	0.43±0.502	0.36±0.485	0.43±0.501	0.50±0.506$^{\&}$
Cube drawing	0.57±0.502	0.49±0.507	0.60±0.497	0.45±0.504	0.48±0.505	0.57±0.501
Clock drawing experiment	1.97±0.923	1.94±0.906	1.97±0.891	2.07±0.973	2.26±0.701$^{\&}$	2.38±0.661$^{\&}$
Nominate	2.40±0.736	2.43±0.739	2.46±0.741	2.57±0.668	2.55±0.633	2.57±0.590
Attention	3.94±1.327	3.60±1.265$^{\&}$	3.63±1.239$^{\&}$	3.81±1.254	4.12±1.064$^{\&}$	4.36±0.958$^{\#\&}$
Language repetition	0.74±0.611	0.71±0.667	0.74±0.657	0.98±0.643	1.02±0.680$^{\#}$	1.14±0.683$^{\&\#*}$
Language fluency	0.77±0.426	0.80±0.406	0.83±0.382	0.74±0.445	0.76±0.431	0.83±0.377
Abstract	0.26±0.443	0.23±0.426	0.29±0.458	0.26±0.497	0.29±0.508	0.31±0.517
Delayed memory	0.91±0.853	0.86±0.879	0.83±0.985	0.67±0.879	1.57±0.914$^{\#\&}$	1.88±0.942$^{\#\&*}$
Orientation	5.29±0.710	5.14±0.692	5.14±0.733	5.05±0.825	5.26±0.767	5.12±0.670

Table 2: Inpatient baseline and MoCA score sheet at one month and six months of follow-up.
$^{\#}$represents comparison with the control group, P<0.05. $^{\&}$represents intra-group comparison with baseline, P<0.05. *represents intra-group comparison with one month of follow-up, P<0.05.

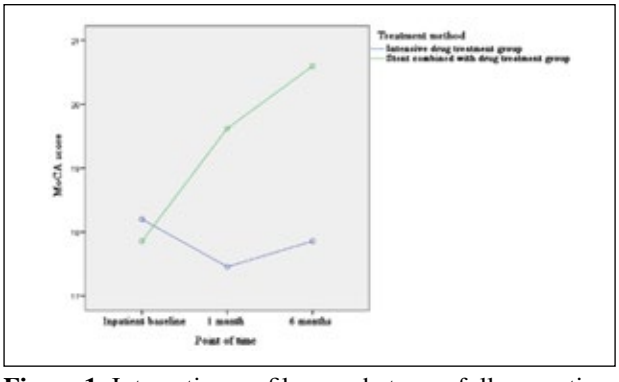

Figure 1: Interactive profilogram between follow-up time points and treatment methods.

In all cognitive domains, improvement was observed at the one-month and six-month follow-up periods in the stent combined with drug treatment group in speech repetition and delayed recall scores compared to the intensive drug treatment group.

At six months of follow-up, attention was also beneficial compared to the intensive drug treatment group. In the drug treatment group, attention decreased by 0.343 (95% confidence interval: 0.053, 0.632, P = 0.015) and 0.314 (95% confidence interval 0.028, 0.600, P = 0.026) compared with the baseline during the follow-up period of one month and six months, respectively. There was no statistical difference in the score of the cognitive domain.

In the stenting combined with drug treatment group, follow-up at one month and six months showed that the clock drawing test, attention and delayed recall scores were higher than those in the baseline (P<0.05). Alternating connection was also found to benefit from the baseline at six months of follow-up (P<0.05).

Comparison of MoCA total score and cognitive domain score at different time points in the perfusion subgroup

According to the different perfusion states determined before the operation, the stenting combined with drug treatment group was divided into a normal perfusion group and an abnormal perfusion group. The total MoCA score in the two groups at different time points is shown in Table 3.

As shown in Figure 2, there also was an interaction between different perfusion states and time points (F = 14.607, P<0.001). The total MoCA score of the abnormal perfusion group was 4.625 lower than that of the normal perfusion group (95% confidence interval: 2.320, 6.930, P<0.001) before operation. There was no statistical difference in the total score between the two groups at six months of follow-up (p = 0.07). In the normal perfusion group, there was no statistical difference between the follow-up at one month and the hospitalization baseline (P = 0.913). The follow-up at six months was 1.000 (95% confidence interval: 0.299, 1.701, P = 0.003) higher than that at one month and 1.222 higher than the hospitalization baseline (95% confidence interval: 0.005, 2.439, P = 0.049), respectively. In the abnormal perfusion group, the follow-up at one month was 2.917 higher than the hospitalization baseline (95% confidence interval: 2.109, 3.725).

The follow-up at six months was 0.958 higher than at one month (95% confidence interval: 0.351,

1.565, P<0.001) and 3.875 higher than the hospitalization baseline (95% confidence interval: 2.821, 4.929, P<0.001), respectively.

Comparing the total score between the two groups, the hospitalization baseline of the abnormal perfusion group was 4.625 lower than the normal perfusion group (95% confidence interval: 2.320, 6.930, P<0.001). There was no difference between the two groups at the one-month and six-month follow-up (P>0.05).

MoCA score	CT normal perfusion group (N=18)			CT abnormal perfusion group (N=24)		
	Before operation	1 month after operation	6 months after operation	Before operation	1 month after operation	6 months after operation
Total score	20.50±3.730	20.72±3.357	21.72±2.866$^{\&,*}$	15.88±3.603$^{\#}$	18.79±3.526$^{\&}$	19.75±3.745$^{\&,*}$
Alternating connection	0.56±0.511	0.61±0.502	0.61±0.502	0.21±0.41$^{\#}$	0.29±0.464$^{\#}$	0.42±0.504$^{\&}$
Cube drawing	0.67±0.485	0.67±0.485	0.67±0.485	0.29±0.46$^{\#}$	0.33±0.48$^{\#}$	0.50±0.511$^{\&,*}$
Clock drawing experiment	2.61±0.698	2.67±0.594	2.72±0.575	1.67±0.963$^{\#}$	1.96±0.624$^{\#\&}$	2.13±0.612$^{\#\&}$
Nominate	2.72±0.461	2.67±0.485	2.67±0.485	2.46±0.779	2.46±0.721	2.67±0.485
Attention	4.17±1.150	4.11±1.079	4.56±0.705*	3.54±1.285	4.12±1.07$^{\&}$	4.21±1.10$^{\&}$
Language repetition	1.22±0.548	1.06±0.639	1.22±0.647	0.79±0.658$^{\#}$	1.00±0.722	1.08±0.71$^{\&}$
Language fluency	0.83±0.383	0.83±0.383	0.89±0.323	0.67±0.482	0.71±0.464	0.79±0.415
Abstract	0.39±0.502	0.44±0.511	0.39±0.502	0.17±0.482	0.17±0.482	0.25±0.532
Delayed memory	1.110.963	1.61±1.037$^{\&}$	1.94±0.725$^{\&,*}$	0.33±0.637$^{\#}$	1.54±0.83$^{\&}$	1.83±1.09$^{\&}$
Orientation	5.39±0.502	5.33±0.767	5.22±0.548	4.79±0.932$^{\#}$	5.21±0.77$^{\&}$	5.04±0.751

Table 3: Analysis of MoCA scores before operation, one month, and six months after operation in the perfusion subgroup.

$^{\#}$represents comparison with the control group, P<0.05. &represents intra-group comparison with baseline, P<0.05. *represents intra-group comparison with one month of follow-up, P<0.05.

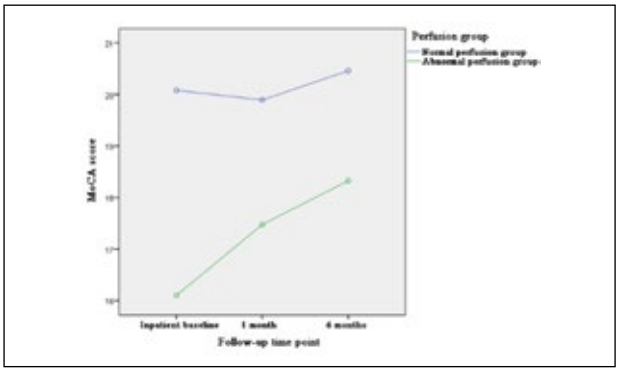

Figure 2: Interactive profilogram between follow-up time points and different perfusion groups.

In the cognitive domain, there were differences between the two groups before the operation in alternating connection, cube drawing, the clock drawing experiment, language repetition, delayed recall and orientation (P<0.05). After six months of follow-up, the clock drawing experiment in the abnormal perfusion group was only 0.597 (95% CI: 0.221, 0.973, P = 0.003) lower than that of the normal perfusion group, and there were no differences in the other cognitive domains.

Discussion

At present, there is a lack of clinical research on the effects of different treatments on cognitive function in symptomatic intracranial atherosclerotic stenosis. To our knowledge, this study is the first to compare the effects of intensive drug treatment and stenting combined with drug treatment on cognitive function in patients with symptomatic middle cerebral artery stenosis with cognitive dysfunction, as well as to conduct subgroup analysis of different cerebral perfusion states before operation.

The SAMMPRIS study used MoCA scores as a secondary end point to evaluate differences in the effects of intensive drug treatment and stenting combined with drug treatment on cognitive function.

In this study, all patients with cerebral vascular events (cerebral infarction, TIA, intracranial haemorrhage) were excluded during each follow-up period. The total number of cases included the following: baseline (183 vs 183), 4 months (152 vs 141), 12 months (129 vs 124), and at the end of the study (104 vs 95). The results showed that there was no difference in the total MoCA score between the two groups at the above four time points, but the total MoCA score was higher than the baseline score at the last three follow-up periods (P<0.05).

The SAMMPRIS study showed that the stenting treatment group had no advantage over the drug treatment group in improving cognitive function for those who had no cerebrovascular events during the follow-up period[13]. However, the study has the following shortcomings: Although the SAMMPRIS study was randomly included in the study population, for the MoCA analysis, retrospective selection of cases was based on whether there were cerebrovascular events during the follow-up period, and the clinical baseline characteristics of the two groups were lack of randomness. In non-random cases, the effect of non-vascular factors on cognitive function was not taken into account, and this conclusion may underestimate the contribution of intracranial artery stenting in improving cognitive function in some patients. Because the SMMPRIS study was associated with a high incidence of adverse events in the stenting combined with drug treatment group, all adverse

events were excluded from the analysis to reduce the impact of these events on the evaluation of cognitive function. We believe that when studying the effect of stent therapy on cognitive function, the follow-up stroke events on cognition function should be taken into account. In addition, the case of the operation should be selected reasonably, and the operation method should be standardized with a view to reducing the incidence of adverse events, which has greater clinical guiding significance. The hypoperfusion state of brain tissue is closely related to the occurrence and development of cognitive impairment[18]. However, some studies suggest that cognitive impairment due to hypoperfusion may be reversible[19]. Stent-assisted angioplasty can significantly improve perfusion in patients with hemodynamic disorders, but the study failed to perform a subgroup analysis of perfusion factors.

In view of these problems, our research has the following advantages and characteristics: Some of the non-vascular factors that can affect cognitive function were excluded from the screening exclusion criteria. At present, a variety of non-vascular factors are known to affect cognitive function[20], including advanced age, severe cardiac insufficiency, obstructive sleep apnoea syndrome, depression and some nervous system diseases[21, 22].

These diseases can affect the evaluation of cognitive function in the two groups of treatment methods. By reviewing the case data and evaluating the Hachiski ischemic scale and Hamilton depression scale at the same time, excluding the interference to the above situation, it is helpful to analyse the different effects of the two treatment methods on cognitive function in the cognitive dysfunction dominated by the responsible middle cerebral artery stenosis. The effect of severe white matter high signal on cognitive function was excluded, since high signal intensity in white matter was considered to be an important cause of vascular cognitive impairment and dementia[23]. Some studies suggest that intracranial atherosclerotic stenosis is closely related to severe white matter high signal[24].

Although there is no report of the effect of the white matter high signal on cognitive function after intracranial artery stenting, the high signal burden of the white matter before the operation can increase perioperative complications and decrease cognitive function after carotid artery recanalization, which has been confirmed by many studies[25-27]. Therefore, as carotid recanalization studies have shown, excluding patients with severe WMH at the time of selection may screen out those who can benefit from the stenting treatment group.

In addition, in this study the surgical treatment procedure was optimized to reduce perioperative adverse events. The SMPRIS study showed that the adverse event rate was 14.9% in the 30-day follow-up period in the stenting group. The safety of stenting therapy is questionable, which hinders the development of intracranial artery stenting. The short average operation time (average 7 days) and the lack of experience were important reasons for the high rate of the above adverse events. Stroke events during postoperative follow-up can also lead to a decrease in cognitive function. Reducing the incidence of postoperative stroke and improving the safety of operations are the foundation for improving postoperative cognitive impairment. First, the operation took place more than 2 weeks after ischemic stroke (TIA patients were unlimited). Some studies compared the difference in the incidence of adverse events (including stroke and death) after stent implantation at different time points within two weeks and found that the incidence of adverse events mentioned above was lower during long-term follow-up (8.1% vs. 21.9%, p=0.035)[28]. Secondly, the balloon angioplasty protocol was optimized. Most of the perioperative ischemic stroke events in the SAMMRPIS study were caused by occlusion of perforating artery[29]. The main causes were related to the strategy of balloon dilatation, size selection, dilatation pressure and time. We adopted a sub-satisfactory balloon expansion strategy: the maximum balloon diameter was 60-80% of the diameter of the responsible blood vessel, the expansion pressure was avoided, the expansion time could be prolonged, and the occurrence of an ischemic stroke in the perioperative period could be reduced. The therapeutic effect of the above strategies has also been further confirmed in other relevant studies[30, 31]. The subgroup analysis was carried out in the stenting treatment group with different perfusion states at the preoperative baseline, with the aim of evaluating whether different perfusion states from baseline could benefit from stenting treatment and the differences in the characteristics of MoCA scores during their follow-up period.

In this study, we found that during the six months of follow-up, stenting combined with drug treatment could improve cognitive impairment in patients with symptomatic middle cerebral artery stenosis with cognitive impairment compared with intensive drug treatment, mainly in the total MoCA score, language repetition, attention and delayed recall. However, no

improvement in cognitive function was found before and after intensive drug treatment. In the total MoCA score, the trend profile of the two treatments in addition to the time points of follow-up are shown in Figure 1. The intensive drug treatment group showed a decrease in the follow-up period at one month and an increase in the follow-up period in six months. The reasons for this may include the time-dependence of the intensive drug regimen on the treatment of intracranial arterial stenosis, the improvement of the degree of intracranial arterial stenosis by using drugs for one month and the limited reduction effect of the stroke recurrent risk[32] and high incidence (11.4%) of recurrent stroke within one month follow-up; all of these decreased the overall cognitive level at one month follow-up.[2] The management of related risk factors (such as hypertension, diabetes, hypercholesteremia, smoking history) also takes a long time to improve the cognitive function, and the benefit is limited in a short period of time[33].

Few research studies to date have examined cognitive function in patients with symptomatic middle cerebral artery stenting. Our results suggest that both the normal perfusion group and the low perfusion group can benefit from stenting. We believe that the normal perfusion group can benefit from the operation similar to the intensive drug treatment group based on reasonable management of cerebrovascular disease- and cognitive impairment-related risk factors[33]. Secondly, no stroke-related adverse events occurred during the follow-up period in the normal perfusion group, which avoided the deterioration of cognitive function after operation—an important benefit. The abnormal perfusion group benefited more from an improvement in the low perfusion state of the brain tissue. A study of carotid stenting has also shown cognitive function benefits by improving perfusion status[34]. It was found that in terms of the extent of the benefit, the abnormal perfusion group showed a significantly greater benefit than the normal perfusion group (3.875 vs. 1.222), and the two subgroups were different at the point of the benefit event. The benefit was observed in the abnormal perfusion group at one month and six months after operation, while no benefit was found in the normal perfusion group at one month after operation, and the benefit was not seen until six months after operation[35, 36].

We believe that the causes of cognitive impairment in the normal perfusion group may be related to the occurrence of ischemic stroke, the burden of cerebellar vascular disease and the poor management of various risk factors before operation. However, the improvement of cognitive function needs to be followed up for a greater period of time. During the six-month follow-up period, the limitation of the effect leads to the limited degree of benefit. In the abnormal perfusion group, the reasons for the benefits could be seen in a short period of time since the recovery of cerebral tissue perfusion status is immediate. This can improve the oxidative stress response of cerebral blood vessels, neuron energy metabolism disorders and central cholinergic and monoaminergic neurotransmitter system dysfunction in a short time[37, 38]. However, this finding needs to be confirmed by additional clinical research.

However, there are limitations in our research. First of all, as a single-centre retrospective study, the sample size was small, and there was bias in patient selection. Second, there was a certain loss-of-access rate, while no asymptomatic cerebral infarction could be found during the follow-up, and the incidence of stroke events during the patients' follow-up period was underestimated.

Third, it cannot well control and monitor drug use and risk factors management. Fourth, the follow-up time in this study was short, and partial middle cerebral artery stent restenosis occurred from six months to one year after operation. In addition, our sub-satisfactory balloon dilatation strategy may increase the occurrence of long-term restenosis, thus affecting cognitive function, which needs to be followed up at a later stage.

Conclusion

Although there were many limitations in this study, it was determined that after a reasonable design of the research scheme, compared with drug therapy, intracranial artery stenting can improve the cognitive function of patients with intracranial artery stenosis accompanied by cognitive impairment, especially in patients with hypoperfusion. However, these findings require confirmation by prospective, randomized controlled studies.

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