The role of atorvastatin in collateral circulation formation induced by encephaloduroarteriosynangiosis: a prospective trial

*Qian-Nan Wang, PhD,¹ Xiang-Yang Bao, MS,² Zheng-Xing Zou, MD,² Xiao-Peng Wang, MD,² Qian Zhang, MS,² De-Sheng Li, PhD,² Ya-Qun Zhao, PhD,¹ and Lian Duan, PhD²

¹Department of Neurosurgery, Chinese PLA General Hospital (former Department of Neurosurgery, the Eighth Medical Center of Chinese PLA General Hospital); and ²Department of Neurosurgery, Chinese PLA General Hospital (former Department of Neurosurgery, the Fifth Medical Center of Chinese PLA General Hospital), Beijing, China

OBJECTIVE This prospective study was designed to confirm the role of atorvastatin in collateral circulation formation induced by encephaloduroarteriosynangiosis (EDAS) in patients with moyamoya disease (MMD).

METHODS Patients who were diagnosed with MMD at the Department of Neurosurgery in the Fifth Medical Center of Chinese PLA General Hospital, Beijing, China, between June 2017 and May 2018 were included. Blood samples were obtained from an antecubital vein and were analyzed using flow cytometry. Endothelial progenitor cells (EPCs) were defined as CD34^{br}CD133⁺CD45^{dim}KDR⁺. All patients included in the study underwent EDAS. Patients voluntarily chose whether to undergo atorvastatin treatment after EDAS. The correlation between atorvastatin and good postoperative collateral circulation was evaluated.

RESULTS A total of 106 patients with MMD were included in this study. Fifty-three patients (50%) received atorvastatin treatment. The baseline characteristics did not display statistically significant differences between the atorvastatin-treated and non-atorvastatin groups. Seventy-eight (42.9%) of the 182 hemispheres investigated postoperatively were classified as grade A collateral circulation, 47 (25.8%) as grade B, and 57 (31.3%) as grade C. Multivariate analysis revealed that only atorvastatin was significantly correlated with good collateral circulation after EDAS ($p = 0.041$).

CONCLUSIONS The results of this prospective clinical trial have indicated that atorvastatin administered at 20 mg daily is safe and effective for the formation of postoperative collateral induced by EDAS.

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KEYWORDS moyamoya; encephaloduroarteriosynangiosis; atorvastatin

MOYAMOYA disease (MMD) is a chronic progressive cerebrovascular disease of unknown etiology. This disease is usually characterized by bilateral internal carotid artery stenosis or occlusion, accompanied by the formation of abnormal vascular network.^{1,2}

Revascularization surgery for symptomatic MMD is considered the standard treatment for preventing further stroke. Encephaloduroarteriosynangiosis (EDAS) is one of the most commonly used indirect vascular reconstruction methods.^{3–7} However, we found that about 20% of patients had poor postoperative collateral circulation in our previous long-term follow-up studies.^{8,9} A recent study by our center showed that the formation of collateral vessels in

EDAS is primarily driven by angiogenesis, and that the endothelial progenitor cell (EPC) count may be the most critical factor for promoting collateral circulation.¹⁰

Studies have shown that statins can effectively reduce the incidence of death and ischemic cardiovascular events in patients with coronary heart disease by reducing cholesterol.^{11–13} Further animal experiments have shown that statins can also affect the mobilization, proliferation, chemotaxis, and apoptosis of EPCs.¹⁴ Importantly, they may suggest that the mobilization of EPCs by statins might represent a useful strategy for clinical therapy of MMD after EDAS. Therefore, we designed this prospective study to confirm the role of atorvastatin in collateral circulation formation induced by EDAS in patients with MMD.

ABBREVIATIONS DSC-MRI = dynamic susceptibility contrast–MRI; EDAS = encephaloduroarteriosynangiosis; EPC = endothelial progenitor cell; MCA = middle cerebral artery; MMD = moyamoya disease; PBMC = peripheral blood mononuclear cell; PCI = posterior circulation involvement; TTP = time to peak.

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* Q.N.W. and X.Y.B. contributed equally to this work and share first authorship. D.S.L. and Y.Q.Z. contributed equally to this work and share senior authorship.

FIG. 1. Flow diagram of this study.

Methods

Patient Selection

Patients who were diagnosed with MMD at the Department of Neurosurgery in the Fifth Medical Center of Chinese PLA General Hospital, Beijing, China, between June 2017 and May 2018 were included in this study (clinical trial registration no. NCT03613701 [clinicaltrials.gov]). The inclusion and exclusion criteria of MMD diagnosis are referred to in previous literature.^{15–17} All patients were aged ≥ 18 years. All patients were evaluated for liver and kidney function before being included in the study, and patients with abnormal liver or kidney function were excluded.

Study Design

A flow diagram of the study is shown in Fig. 1. A blood sample from each patient was collected before revascularization. All peripheral blood samples were analyzed by flow cytometry.¹⁸ EPCs were defined as $CD34^{bri}CD133^{+}CD45^{dim}KDR^{+}$. The EPC count was reported as a percentage of the peripheral blood mononuclear cells (PBMCs). All patients with MMD included in the study underwent EDAS. The specific surgical methods were referred to in previous reports.¹⁹

After surgery, the researchers fully explained the intention of this trial and the possible adverse reactions of atorvastatin treatment to all patients. Patients voluntarily chose whether to take atorvastatin; patients who declined to take atorvastatin were included in the control group. Atorvastatin (Pfizer) was administered at 20 mg per night for 8 weeks.^{20–22} Laboratory tests of liver and kidney function were performed after 8 weeks of medication. Any adverse reactions that occurred were recorded by the follow-up doctor.

DSA images were obtained 6 months after EDAS. The development of collateral circulation of the middle cerebral artery (MCA) through bypass was graded according to the system described by Matsushima et al.²³

Clinical Data

The clinical data obtained in this study included sex, age, initial symptoms, hypertension, diabetes mellitus, preoperative angiographic stage, unilateral disease, and posterior circulation involvement (PCI). The angiographic stage was evaluated according to the Suzuki classification.² The angiographic collateral grade was evaluated according to the system described in our recent study.²⁴ The grading score was based on the collateral circulation and

TABLE 1. Baseline characteristics of patients with MMD in the study

Variable	Value
Mean age, yrs	40.5 ± 9.8
Female sex	62 (58.5)
Initial symptoms	
TIA	37 (34.9)
Infarction	50 (47.2)
Hemorrhage	19 (17.9)
History of risk factors	
Hypertension	16 (15.1)
Diabetes mellitus	12 (11.3)
Smoking or drinking	19 (17.9)
Unilateral lesions	30 (28.3)
Atorvastatin use	53 (50.0)
Mean EPCs before EDAS	0.061% ± 0.053%

TIA = transient ischemic attack.

Values represent the number of patients (%) or mean ± SD.

ranged from 1 to 12 with the following considerations: 1) the anatomy extent of pial collateral blood from the posterior cerebral artery (PCA) territory to the anterior cerebral artery (ACA) and MCA territory on the delayed venous phase; and 2) the basal brain perforators and moyamoya vessels, which were defined using the Suzuki stage. The three collateral circulation status stages in MMD were defined as follows: scores from 1 to 4 were defined as a poor collateral status (stage I), scores from 5 to 8 were defined as a fair collateral status (stage II), and scores from 9 to 12 were defined as a good collateral status (stage III). All angiography images were reviewed by two experienced readers (X.Y.B. and Q.N.W.) who were blinded to the angiography results and clinical details. Any differences in their observations were resolved by consensus. The cerebral hemodynamic status was assessed by dynamic susceptibility contrast–MRI (DSC–MRI) using a MAGNETOM Skyra 3T MRI scanner (Siemens). The acquired DSC–MRI images were processed using a post-processing workstation (Syngo Via 20, Siemens) and analyzed with the MR Neuro-Perfusion software (Siemens). We used time to peak (TTP), or the time at which contrast level reaches its maximum, and hemodynamic parameter calculated by MR perfusion to evaluate the hemodynamic status of the patients.

Statistical Analysis

The chi-square test was used to analyze categorical variables, and the independent Student t-test or ANOVA was used to compare continuous variables. The Mann-Whitney U-test or the Kruskal-Wallis test was performed on variables that did not follow a normal distribution. Univariate analysis was used to assess the correlation between age, sex, initial symptoms at diagnosis, collateral grade, PCI, atorvastatin use, and the EPC count and collateral circulation after EDAS. The variables with significant as-

sociation ($p < 0.05$) were selected and subjected to multiple linear regression analysis. A p value < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 106 patients with MMD were included in this study. The clinical characteristics of the patients are summarized in Table 1. The mean age at symptom onset was $40.5 \pm \text{SD } 9.8$ years, and there were 62 female and 44 male patients. Among the patients with MMD, a history of hypertension was reported in 16 patients (15.1%), a history of diabetes in 12 (11.3%), and previous tobacco or alcohol use in 19 (17.9%). As the initial symptoms, 37 patients (34.9%) exhibited transient ischemic attacks, 50 patients (47.2%) exhibited infarction symptoms, and 19 patients (17.9%) exhibited hemorrhagic symptoms. Thirty patients exhibited unilateral disease. The EPC count in the patients with MMD was $0.061\% \pm 0.053\%$ (expressed as the percentage of PBMCs). According to study design, 53 (50%) patients received atorvastatin treatment voluntarily.

Table 2 shows the comparison of baseline characteristics and angiographic outcome between the atorvastatin and control groups. Baseline characteristics included age at symptom onset, sex, history of risk factors, EPC count before EDAS, unilateral lesions, symptoms in hemispheres, PCI, Suzuki stage, TTP delay, and collateral grade; none displayed statistically significant differences between the two groups ($p > 0.05$).

Association of Postoperative Collateral Formation With Atorvastatin

Because of the unilateral lesion in 30 patients, a total of 182 hemispheres were treated with EDAS. Cerebral arteriography was performed 6 months after EDAS to assess the efficacy of synangiosis and to guide subsequent disease management. Seventy-eight (42.9%) of the 182 hemispheres investigated were classified as grade A collateral circulation, 47 (25.8%) as grade B, and 57 (31.3%) as grade C.

Results of the univariate analysis are summarized in Table 3. Patients who were treated with atorvastatin could get better postoperative collateral circulation (grade A or B) than the control group ($p = 0.006$). The postoperative angiographic findings also showed that a good Matsushima grade was correlated with infarction symptoms ($p = 0.034$) and a higher EPC count before EDAS ($p > 0.99$). The variables with significant correlation were subjected to multiple linear regression analysis. The multivariate analysis revealed that only atorvastatin was significantly correlated with good collateral circulation after EDAS ($p = 0.041$).

Figures 2 and 3 show representative patients from each of the two groups. A 50-year-old female whose initial symptom was cerebral infarction had an EPC percentage in peripheral blood of 0.039% before EDAS, which was far below the average level. Atorvastatin was administered regularly after the operation. Excellent collateral circulation was obtained in both hemispheres after 6 months (Fig. 2). In contrast, Fig. 3 shows a 43-year-old

TABLE 2. Comparison of baseline characteristics and angiographic outcome between the atorvastatin and control groups

Variable	Atorvastatin Group (n = 53)	Control Group (n = 53)	p Value
Mean age, yrs	42.4 ± 9.9	38.6 ± 9.3	0.551
Female sex	25 (47.2)	37 (69.8)	0.073
History of risk factors	23 (43.4)	24 (45.3)	0.845
Mean EPCs before EDAS	0.066 ± 0.056%	0.055 ± 0.043%	0.183
Unilateral lesion	15 (28.3)	15 (28.3)	>0.99
Total diseased hemispheres	91	91	
Symptoms in hemispheres			0.254
Asymptomatic	34 (37.3)	31 (34.1)	
TIA	18 (19.8)	25 (27.5)	
Infarction	32 (35.2)	23 (25.3)	
Hemorrhage	7 (7.7)	12 (13.2)	
PCI	19 (20.9)	23 (25.3)	0.482
Suzuki stage			0.805
I	9 (9.9)	8 (8.8)	
II	18 (19.8)	13 (14.3)	
III	18 (19.8)	19 (20.9)	
IV	19 (20.9)	22 (24.2)	
V	15 (16.5)	12 (13.2)	
VI	12 (13.2)	17 (18.7)	
Collateral grade			0.797
Poor (stage I)	35 (38.5)	37 (40.7)	
Fair (stage II)	30 (33.0)	32 (35.2)	
Good (stage III)	26 (28.6)	22 (24.2)	
Mean TTP delay, secs			
Before EDAS	4.55 ± 2.18	3.78 ± 1.98	0.644
6 mos after EDAS	3.41 ± 1.67	3.01 ± 2.41	0.481

Values represent the number of patients (%) or mean ± SD unless indicated otherwise.

male in the control group who also had cerebral infarction as the first symptom and had an EPC percentage of 0.027% before EDAS. Reexamination of cerebral angiography 6 months later indicated poor collateral circulation formation.

Drug Safety and Follow-Up

According to the follow-up laboratory tests, 8 patients (15.1%) presented with mild liver abnormalities and 2 patients (3.8%) with mild kidney abnormalities, but none required treatment.

No patient experienced a severe adverse drug reaction or event, which included the following: death, life-threatening or permanent or significant disability, permanent functional injury to the organs, hospitalization for emergencies, or prolonged hospitalization. During the follow-

up period after EDAS, no patient had cerebral infarction or cerebral hemorrhage caused by MMD.

Discussion

Atorvastatin, as a classic lipid-lowering drug, has been widely used in the cardiovascular field. Moreover, some reports have confirmed that atorvastatin could also promote angiogenesis in models of stroke and brain injury.^{25–27} However, to the best of our knowledge, no studies have reported the use of atorvastatin in the treatment of MMD, and our study may provide a new idea for drug-assisted therapy after indirect revascularization.

In this prospective study, we found that the extent of postoperative collateral formation in patients with atorvastatin treatment was significantly higher than the control group, which means that atorvastatin could help patients have a better surgical outcome. This is of great significance for MMD patients, especially for those with severe cerebral ischemia. Patients can take atorvastatin to further strengthen the formation of postoperative collateral circulation, so as to better prevent the occurrence of stroke in the future.

At present, research on the effect of statins on EPCs in human peripheral blood has been mostly concentrated in the cardiovascular field. It has been confirmed that statins can affect the mobilization, proliferation, chemotaxis, and apoptosis of EPCs.¹⁴ Vasa et al.¹⁴ treated patients with stable coronary heart disease confirmed by arteriography with atorvastatin. The authors found that the number of circulating EPCs increased significantly, and that the migration ability of EPCs isolated and cultured from peripheral blood significantly enhanced. Schömig et al.²⁸ observed in patients with acute myocardial infarction that the number of circulating EPCs in the peripheral blood was positively correlated with statins. Landmesser et al.²⁹ also observed in patients with chronic heart failure that after 4 weeks of treatment with simvastatin 10 mg/day, the number of EPCs isolated and cultured from peripheral blood increased significantly. The aforementioned studies have shown that statins can significantly promote the number and function of EPCs; however, the specific mechanism of atorvastatin that promotes angiogenesis is not yet clear. Based on the results in previous studies, we speculate that statin-induced stimulation of the Akt/endothelial nitric oxide synthase pathway might contribute to the observed effects of statins on the functional improvement of EPCs.^{30–34}

It is undeniable that 33.3% of the hemispheres in our study did not achieve good collateral circulation after atorvastatin treatment. The process of angiogenesis is affected by many factors, and EPCs are only one of the important components. In future efforts, we will carry out a multicenter, large-sample, prospective randomized controlled study to further clarify the role of atorvastatin in patients with MMD after surgery. The specific molecular biology mechanism should also be explored at the same time.

Limitations

This study has several limitations. First, it is not a prospective randomized controlled study. Patients voluntarily

TABLE 3. Association of postoperative collateral formation with atorvastatin

Variable	Grade A (n = 78)	Grade B (n = 47)	Grade C (n = 57)	p Value
Mean age, yrs	41.1 ± 9.8	38.7 ± 9.7	41.2 ± 9.8	0.997
Symptoms in hemispheres				0.034
Asymptomatic	26 (33.3)	16 (34.0)	23 (40.4)	
TIA	21 (26.9)	11 (23.4)	11 (19.3)	
Infarction	27 (34.6)	17 (36.2)	11 (19.3)	
Hemorrhage	4 (5.1)	3 (6.4)	12 (21.1)	
PCI	18 (23.1)	13 (27.7)	11 (19.3)	0.602
Collateral grade				0.194
Poor (stage I)	35 (44.9)	20 (42.6)	17 (29.8)	
Fair (stage II)	28 (35.9)	15 (31.9)	19 (33.3)	
Good (stage III)	15 (19.2)	12 (25.5)	21 (36.8)	
Atorvastatin use				0.006
Yes	42 (53.8)	30 (63.8)	19 (33.3)	
No	36 (46.2)	17 (36.2)	38 (66.7)	
Mean EPCs before EDAS	0.082 ± 0.063%	0.064 ± 0.033%	0.043 ± 0.035%	<0.001

Values represent the number of patients (%) or mean ± SD unless indicated otherwise.

chose whether to undergo atorvastatin treatment or not, which may cause statistical bias on the results of the experiment. Second, our study was conducted at a single center, the sample size was small, and it included a pa-

tient population that lacked heterogeneity. Third, due to geographic or economic reasons, some patients underwent cerebral angiography review in other hospitals. Therefore, we could not detect the number of EPCs in peripheral

FIG. 2. A patient from the atorvastatin group. **A:** Flow cytometry analysis of a 50-year-old female who had cerebral infarction as the first symptom and an EPC percentage in the peripheral blood measured before EDAS of 0.039%, which was far below the average level. **B and C:** Bilateral internal carotid angiograms, lateral views, before EDAS. Atorvastatin was administered regularly after the surgery. **D and E:** Excellent collateral circulation induced by EDAS (Matsushima grade A) was obtained in both hemispheres after 6 months. -A = area; APC = allophycocyanin; Comp = compensation; FITC = fluorescein isothiocyanate; FSC = forward scatter; PE = phycoerythrin; PerCP = peridinin chlorophyll protein complex; SSC = side scatter.

FIG. 3. A patient from the control group. **A:** Flow cytometry analysis of a 43-year-old male who also had cerebral infarction as the first symptom and an EPC percentage of 0.027% before EDAS. **B and C:** Bilateral internal carotid angiograms, lateral views, before EDAS. **D and E:** Reexamination of cerebral angiography 6 months later indicated poor collateral circulation formation induced by EDAS (Matsushima grade C).

blood 6 months after surgery in all study patients. In addition, the molecular mechanism of atorvastatin affecting the formation of surgical collateral circulation still needs to be further explored.

Conclusions

This prospective clinical trial finds that atorvastatin administered at 20 mg daily is safe and effective for the formation of postoperative collateral induced by EDAS. Patients with severe ischemic symptoms are more likely to obtain a better surgical outcome.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Duan, Zhao. Acquisition of data: QN Wang, Bao, XP Wang, Zhang. Drafting the article: QN Wang, Li. Critically revising the article: Zou. Statistical analysis: Zou, Li.

Correspondence

Lian Duan: Chinese PLA General Hospital, Beijing, China. duanlian307@sina.com.