Am J Transl Res 2022;14(10):7128-7134
www.ajtr.org /ISSN:1943-8141/AJTR0144118

Original Article

Stenting for elderly patients with internal carotid artery stenosis: analysis of clinical efficacy

Ziming Ye*, Chao Huang*, Lizhou Wang, Shi Zhou, Xing Li, Min Xu

*Department of Interventional Radiology, Affiliated Hospital of Guizhou Medical University, Guiyang 550004, Guizhou, China. *Equal contributors.*

Received May 13, 2022; Accepted August 7, 2022; Epub October 15, 2022; Published October 30, 2022

Abstract: Objective: This retrospective study aimed to investigate the clinical efficacy and safety of carotid artery stenting (CAS) in elderly patients with internal carotid artery stenosis (ICS). Methods: Ninety elderly ICS patients admitted between January 2019 - July 2021 were selected and divided into a control group and a research group according to different treatment method. The 42 cases in the control group were received carotid endarterectomy and the 48 cases in the research group were treated with CAS. The effects of the two intervention methods on the National Institutes of Health Stroke Scale (NIHSS) score, complication rate, oxidative stress, inflammatory cytokines and cognitive function were observed and evaluated. Results: Compared to baseline (before treatment), the research group showed significantly reduced scores of NIHSS and activities of daily living, appreciably decreased levels of malonaldehyde, interleukin-6 and high-sensitivity C-reactive-protein, but increased superoxide dismutase, Rapid Verbal Retrieve score and Digit Span Test score after treatment. Also, the same trends were found when comparing the above results with those of the control group after treatment. The two groups showed a comparable complication rate. Conclusions: The above data indicate a definite clinical efficacy and a favorable safety profile of CAS for ICS in the elderly. CAS can effectively reduce the oxidative stress and inflammatory cytokines of patients and enhance their cognitive function.

Keywords: Carotid artery stenting, internal carotid artery stenosis, curative effect, safety

Introduction

As one of the main cerebral vessels, the carotid artery is responsible for transporting blood from the heart to head, neck, and face [1]. Internal carotid artery stenosis (ICS), with atherosclerosis as its main cause and arteritis, arterial dissection, and cervical radiotherapy as secondary predisposing factors, is the main cause of cerebral ischemia events and has a predilection for the elderly [2, 3]. The risk of cerebral ischemic events becomes elevated if the degree of ICS exceeds 50% [4]. This disease can be symptomatic or asymptomatic, but asymptomatic patients will eventually develop symptoms. Therefore, it is of great significance to analyze the therapeutic effect of ICS from the perspective of surgical treatment for asymptomatic patients to optimize disease management [5-7].

Currently, the surgical strategy for ICS is mainly to remove thickened intima and atherosclerotic plaque by stripping the carotid intima, thus alleviating vascular stenosis and restoring normal blood supply to the brain [8]. Both carotid endarterectomy (CEA) and carotid artery stenting (CAS) have been shown to be effective in treating patients with severe ICS, either symptomatic or asymptomatic [9]. The study of Marsman et al. [10] has pointed out that CEA is a preferred treatment for symptomatic patients with > 50% degree of ICS. It also helps prevent ischemic stroke during treatment for ICS, but still has a risk of postoperative stroke of 2-5% [11]. Nowadays, the effectiveness of CAS in treating ICS has been increasingly recognized in studies. For example, Zhang et al. [12] reported that CAS could basically relieve the symptoms of patients with ICS, increase intracranial blood supply, alleviate or correct hypoperfusion, and gradually eliminate harmful substances present during ischemia and excitatory amino acids, thus improving patients' cognitive function (CF). There is also a single case report by Ryu [13], which applied CAS for an elderly patient with ICS of a persistent primitive sublingual artery, and found that the treatment not only prevented distal embolism, but also ensured the smooth flow of regional blood flow in both arteries.

In this study, we included 90 elderly patients with ICS for analysis, with the aim to provide novel insight into the management of elderly ICS patients and prevention of complications.

Materials and methods

General data

This retrospective study was conducted after obtaining approval from the Ethics Committee. Elderly ICS patients (n=90) admitted between January 2019 to July 2021 were selected as research participants. Inclusion criteria: patients diagnosed with ICS; patients aged over 60 years old; patients had no operative contraindications and were treatment-naive; patients had no obvious abnormality in brain tissue; patients did not use drugs in the last six months that might affect the results of this study. Exclusion criteria: patients had severe organ dysfunction; patients had intracranial aneurysm or vascular malformation; patients had coagulation dysfunction; patients had serious mental disorders; patients had infectious or immune system diseases; patients had recurrent ICS.

Patients were grouped according to the different treatment methods they received. Those who received CEA were set as a control group (n=42), including 22 men and 20 women, with an average age of (66.74 ± 4.04) years old and a disease course of (3.74 ± 1.77) years. The patients who underwent CAS were set as a research group (n=48), with a male-to-female ratio of 29:19, a mean age of (68.79 ± 5.99) years old and a disease course of (3.81 ± 1.44) years.

Surgical methods

CEA: patients were given general anesthesia, electrocardiogram (ECG) monitoring and dynamic evaluation of blood pressure (BP). The appropriate surgical incision was determined based on the preoperative evaluation of the distance between the distal endarterial plaque and the carotid bifurcation. The common, internal, and external carotid arteries were then exposed by separating anterior carotid tissue layer by layer. Before arterial occlusion intervention, systemic heparinization (Shanghai Yuntai Information Technology Co., Ltd., YTD-0003) was administered intravenously, and the systolic BP was adjusted to be 20 mmHg higher than the basal to prevent intraoperative cerebral hypoperfusion. Then, 7-0 sutures (Henan Zeyuan Medical Equipment Sales Co., Ltd., 8735H 7-0) were used after complete stripping of the intimal plaque. The BP was adjusted to the basal BP after incision suturing, and protamine (Beijing Pufei Biotechnology Co., Ltd., PR1197) and heparin were injected by an iv bolus to neutralize heparin to relieve arterial occlusion.

CAS: patients were given general anesthesia and ECG monitoring. After the puncture of the right femoral artery, an 8F arterial sheath was placed. Following systemic heparinization, the guide tube was placed proximal to the carotid stenosis, the protective umbrella was placed and the balloon was predilated, followed by the placement of self-expanding stent. After positioning, the stent was released, the umbrella was recovered, the guide wire and catheter were withdrawn, and the artery was closed.

Outcome measures

(1) National Institutes of Health Stroke Scale (NIHSS) [14]. The score ranges from 0 points to 42 points and is proportional to neurological impairment.

(2) Safety. Local hematoma, hyperperfusion syndrome, vasovagal reflex, ischemic stroke, lower limb deep venous thrombosis and other adverse events were recorded in both groups.

(3) Oxidative stress (OS) and inflammatory cytokines (ICs). Malonaldehyde (MDA), superoxide dismutase (SOD), interleukin-6 (IL-6) and high-sensitivity C-reactive-protein (hs-CRP) levels in the serum, which was separated from 4 mL of fasting elbow venous blood collected from each patient before and one month after treatment, were measured using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Guang Rui Biological Co., Ltd., elisa2013-0840, 416, 1401, 1497) [15].

(4) CF. Patients' CF was evaluated by the Activities of Daily Living (ADL) Scale, Rapid Verbal Retrieve (RVR) and Digit Span Test (DS)

Table 1. General data of the two groups of patients [n (%), mean ± SD]

Factor	n	Control group (n=42)	Research group (n=48)	χ^2/t	P
Sex				0.589	0.443
Male	51	22 (52.38)	29 (60.42)		
Female	39	20 (47.62)	19 (39.58)		
Average age (years)	90	66.74 ± 4.04	68.79 ± 5.99	1.875	0.064
Course of disease (years)	90	3.74 ± 1.77	3.81 ± 1.44	0.207	0.837
Stenosis of the initial segment of internal carotid artery				0.080	0.777
Without	50	24 (57.14)	26 (54.17)		
With	40	18 (42.86)	22 (45.83)		
Extracranial segment stenosis				0.029	0.866
Without	84	39 (92.86)	45 (93.75)		
With	6	3 (7.14)	3 (6.25)		
Stenosis with atheromatous plaques				0.804	0.370
Without	60	30 (71.43)	30 (62.50)		
With	30	12 (28.57)	18 (37.50)		
Hypertension				0.237	0.626
Without	62	30 (71.43)	32 (66.67)		
With	28	12 (28.57)	16 (33.33)		
Diabetes mellitus				0.947	0.330
Without	53	27 (64.29)	26 (54.17)		
With	37	15 (35.71)	22 (45.83)		
Hyperlipidemia				0.728	0.394
Without	58	29 (69.05)	29 (60.42)		
With	32	13 (30.95)	19 (39.58)		
Stenosis length (mm)				0.459	0.498
< 15	42	18 (42.86)	24 (50.00)		
≥ 15	48	24 (57.14)	24 (50.00)		

[16]. Among them, the ADL score ranges from 20 to 80 points and is directly proportional to cognitive impairment. RVR is mainly used to evaluate long-term memory and language function, while DS to assess attention and immediate memory.

Among these indicators, NIHSS, safety, OS and ICs were primary outcome measures, while ADL, RVR and DS were the secondary ones.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 (Beijing Easybio), and figures were generated by GraphPad Prism 6 (GraphPad Software, San Diego, USA). The Chi-square test was utilized for inter-group comparison of categorical data represented as case/percentage [n (%)]. The quantitative data were expressed as mean ± standard deviation (mean ± SD), and differences between groups and within groups were identified using the independent samples t-test and paired t-test, respectively. $P < 0.05$ was the threshold of significance.

Results

Baseline data

The two groups differed insignificantly in sex, mean age, course of disease, initial segment stenosis of internal carotid artery, extracranial segment stenosis, stenosis with atheromatous plaques, hypertension, diabetes, hyperlipidemia, stenosis length and other baseline data ($P > 0.05$) (**Table 1**).

Influences of two intervention methods on NIHSS score

We used the NIHSS to evaluate the impacts of the two interventions on the clinical outcomes of ICS patients. Our data showed that the pre-

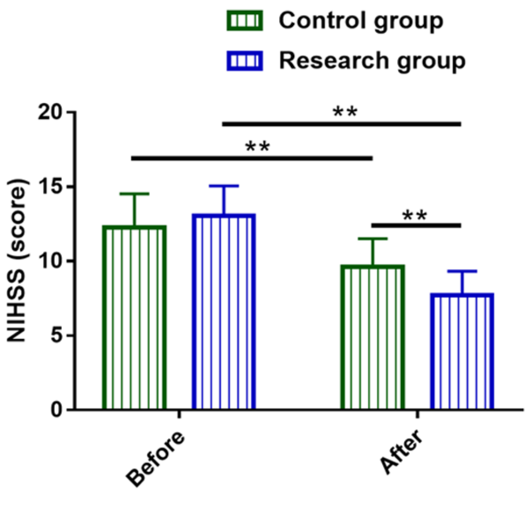

Figure 1. Effects of both intervention methods on NIHSS score. $^{**}P < 0.01$. NIHSS, National Institutes of Health Stroke Scale.

and post-treatment NIHSS scores (points) in the research group were (13.05 ± 2.00) and (7.71 ± 1.61), respectively, while those in the control group were (12.26 ± 2.26) and (9.60 ± 1.90), respectively. The above data showed no statistical difference between the two groups in the NIHSS score before treatment ($P > 0.05$), but markedly reduced scores in both groups after treatment, with lower score in the research group than that in the control group ($P < 0.01$) (**Figure 1**).

Influences of two intervention methods on patient safety

We examined the safety of the two groups of patients to assess the impacts of the two treatments on patient safety. Death, cardiac complications, cranial nerve injury, ischemic stroke and bradycardia/hypotension were observed in 1, 1, 0, 0 and 3 cases, respectively in the research group, while the corresponding cases in the control group were 1, 2, 3, 2 and 0, respectively. The incidence of adverse events was not statistically different between the research group and the control group (10.41% *vs.* 19.05%, $P > 0.05$) (**Table 2**).

Impacts of the two intervention methods on patients' OS

OS values were measured in both groups to analyze the effects of the two surgical procedures on OS. The two groups showed no statistical differences in MDA and SOD before treatment ($P > 0.05$). After intervention, MDA decreased and SOD increased in both groups, and compared to the control group, MDA was lower and SOD was higher in the research group ($P < 0.01$) (**Figure 2**).

Impacts of the two intervention methods on ICs

Pre- and post-treatment ICs were measured to analyze the influences of the two interventions on inflammation. The two groups showed no significant differences in IL-6 and hs-CRP before treatment ($P > 0.05$). After treatment, the ICs were reduced significantly in both groups and were lower in the research group than those in the control group ($P < 0.01$) (**Figure 3**).

Influences of the two intervention methods on patients' CF

Using ADL, RVR, DS scales, the impacts of the two intervention methods on patients' CF were assessed. The data also showed that ADL, RVR, and DS of the two groups were not statistically different before treatment ($P > 0.05$). The post-treatment ADL score in the research group was lower than that before treatment and that in control group after treatment ($P < 0.01$). In addition, the post-treatment RVR and DS scores of research group were significantly elevated and were higher than those of the control group ($P < 0.05$) (**Figure 4**).

Discussion

Internal carotid stenosis (ICS) originates from abnormal narrowing or contraction of the inner surface of the carotid artery, which is mainly manifested as abnormal accumulation of atherosclerotic plaque on the artery wall that leads to blood flow obstruction [17]. This study aims to provide novel insights into ICS treatment.

At present, CAS has developed as a reliable alternative to CEA, and is suitable for symptomatic patients with moderate- and high-grade ICS [18]. Its therapeutic advantage is that it can quickly relieve arterial stenosis and ischemia-related distal vascular hemodynamic abnormalities, and plays a cerebral protective role in cerebrovascular diseases [8]. In our research, ICS patients treated with CEA were included in

Table 2. Adverse events after treatment in the two groups [n (%)]

Category	Control group (n=42)	Research group (n=48)	χ^2 value	*P* value
Death	1 (2.38)	1 (2.08)	-	-
Cardiac complications	2 (4.76)	1 (2.08)	-	-
Cranial nerve injury	3 (7.14)	0 (0.00)	-	-
Ischemic stroke	2 (4.76)	0 (0.00)	-	-
Bradycardia or hypotension	0 (0.00)	3 (6.25)	-	-
Total	8 (19.05)	5 (10.41)	1.350	0.245

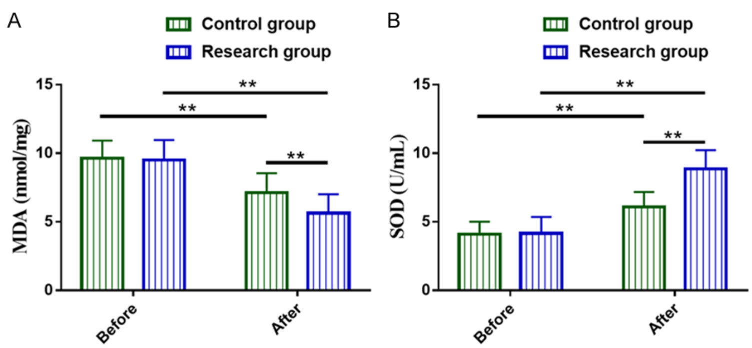

Figure 2. Effects of both intervention methods on the OS of patients. A. Effects of the two intervention methods on MDA of the patients. B. Effects of the two intervention methods on SOD of the patients. Note: $^{**}P < 0.01$. MDA, Malonaldehyde; SOD, superoxide dismutase; OS, oxidative stress.

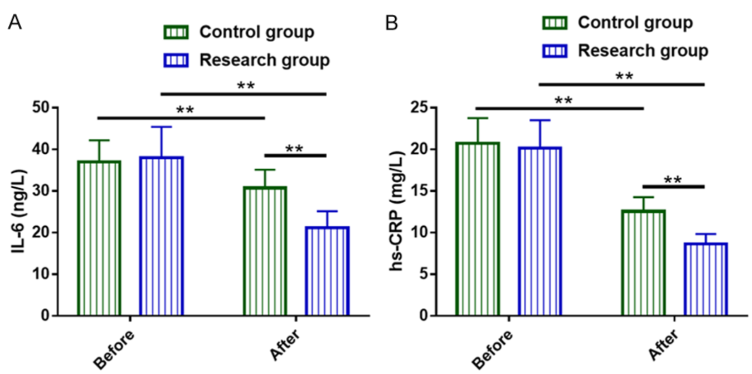

Figure 3. Effects of both intervention methods on the ICs of patients. A. Effects of the 2 intervention methods on IL-6 of the patients. B. Effects of the 2 intervention methods on hs-CRP of the patients. Note: $^{**}P < 0.01$. ICs, inflammatory cytokines; IL-6, interleukin-6; hs-CRP, high-sensitivity C-reactive-protein.

the control group and those who received CAS were assigned to the research group. CAS treatment was found to alleviate nerve defects more significantly in ICS patients than CEA. This was mainly explained by better improvement of NIHSS score in the research group. ICS is known to induce abnormal nerve blood supply and consequently nerve defects, which adversely affects patients' CF [19, 20]. As far as patient safety is concerned, patients in the research group mainly developed bradycardia or hypotension, followed by death and cardiac complications. In the control group, cranial nerve injury was predominant, followed by cardiac complications, ischemic stroke, and death. The statistics on complication rate identified no statistical difference between the two groups, which was similar to the findings of Trystuła M et al. [21]. Apart from that, OS and inflammation are the main pathogenic processes of atherosclerosis-related carotid stenosis, whereby OS can lead to intracranial carotid atherosclerosis and cerebral vascular oxidative damage, while vascular inflammation can induce the generation and deterioration of atherosclerotic plaques in human aorta, carotid artery, brain, and coronary artery [22]. The experimental results of a mouse vascular dementia model established by bilateral common carotid artery stenosis also showed that OS and inflammatory reaction could cause cardiac dysfunction and cognitive impairment in mice [23]. In this study, we also analyzed the impacts of the two interventions on OS, inflammatory response, and CF in patients with ICS. It was confirmed that CAS contributed to more prominent improvement in the above three aspects than CEA intervention in ICS patients, indicating that CAS treatment is more condu-

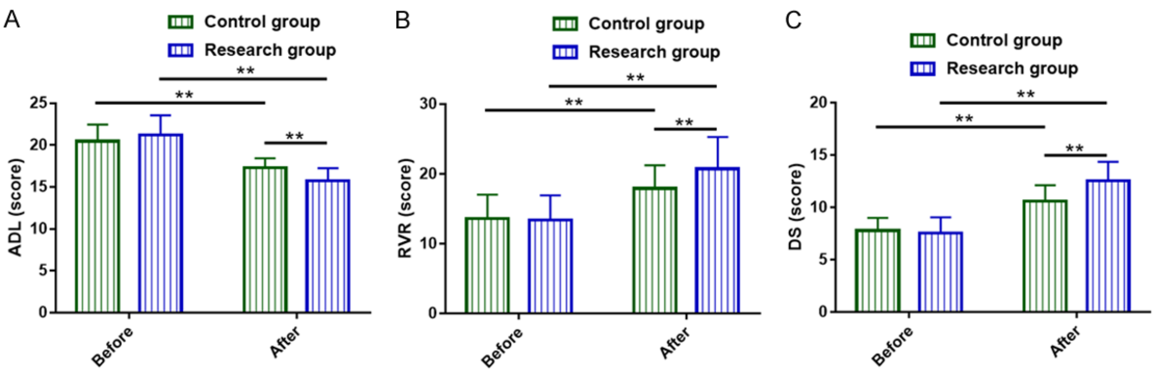

Figure 4. Influences of both intervention methods on patients' CF. A. Effects of the two intervention methods on the ADL score of the patients. B. Effects of the two intervention methods on the RVR score of the patients. C. Effects of the two intervention methods on the DS score of the patients. Note: $^{**}P < 0.01$. CF, cognitive function; ADL, Activities of Daily Living; RVR, Rapid Verbal Retrieve; DS, Digit Span Test.

cive to inhibiting OS, relieving an inflammatory reaction, and improving patients' CF.

This study confirmed that CAS is effective in the treatment of ICS. This method can significantly alleviate nerve defects, OS, and inflammation, and enhance patients' CF, with equivalent safety to CEA. However, this study has several limitations. First, it is a non-randomized and retrospective study. Second, there is no design about patient prognosis, which restricted the understanding of patient outcomes after the two interventions. Third, the sample size of this study is small, so it will be necessary to increase the sample size to further improve the accuracy of experimental results.

To sum up, CAS, as a minimally invasive alternative to CEA, has more advantages in treating elderly ICS patients, mainly because it is more conducive to relieving patients' nerve defects, OS and inflammation, and enhancing their CF, with a safety profile equivalent to CEA.

Acknowledgements

This study was supported by the Cultivate project 2020 for National Natural Science Foundation of China, the Affiliated Hospital of Guizhou Medical University (No. gyfynsfc [2020]-28). The Startup Fund project for Doctor Research, the Affiliated Hospital of Guizhou Medical University (No. gyfybsky-2021-18).

Disclosure of conflict of interest

None.

Address correspondence to: Min Xu and Xing Li, Department of Interventional Radiology, Affiliated Hospital of Guizhou Medical University, No. 28 Guiyi Road, Guiyang 550004, Guizhou, China. Tel: +86-0851-86774195; E-mail: minxu138@126.com (MX); lixing111@sina.com (XL)

References

[1] Liu H, Zhou J, Jiang W and Wang F. Analysis of the diagnostic and prognostic value of miR-9-5p in carotid artery stenosis. Bosn J Basic Med Sci 2021; 21: 724-729.

[2] Khripun AI, Asratian SA, Priamikov AD, Mironkov AB, Suriakhin VS and Gulina LD. Treatment of patients with a cerebral arterial aneurysm and stenosis of the internal carotid artery. Angiol Sosud Khir 2020; 26: 79-84.

[3] Yin Y, Cheng Z, Fu X and Ji S. MicroRNA-375-3p is implicated in carotid artery stenosis by promoting the cell proliferation and migration of vascular smooth muscle cells. BMC Cardiovasc Disord 2021; 21: 518.

[4] Zhang T and Liu R. Dysregulation of miR-637 serves as a diagnostic biomarker in patients with carotid artery stenosis and predicts the occurrence of the cerebral ischemic event. Bioengineered 2021; 12: 8658-8665.

[5] Liu X, Zheng X, Wang Y and Liu J. Dysregulation serum miR-19a-3p is a diagnostic biomarker for asymptomatic carotid artery stenosis and a promising predictor of cerebral ischemia events. Clin Appl Thromb Hemost 2021; 27: 10760296211039287.

[6] Xu S, Wu P, Zhang T, Ji Z, Wang C and Shi H. Prevalence and clinical predictors of intracranial hemorrhage following carotid artery stenting for symptomatic severe carotid stenosis. World Neurosurg 2021; 155: e353-e361.

[7] Li R, Jiang L and Wang X. Aberrant expression of miR-483-5p in patients with asymptomatic carotid artery stenosis and its predictive value for cerebrovascular event occurrence. Exp Ther Med 2021; 22: 1101.

[8] Takao N, Hagiwara Y, Shimizu T, Soga K, Tsuchihashi Y, Otsubo H, Tatsuno K, Takaishi S, Usuki N, Yoshie T, Takada T, Ueda T, Hasegawa Y and Yamano Y. Preprocedural carotid plaque echolucency as a predictor of in-stent intimal restenosis after carotid artery stenting. J Stroke Cerebrovasc Dis 2020; 29: 105339.

[9] Sklinda K, Mruk B, Surowiecka A, Cias M, Paluch L, Andziak P and Walecki J. Role of magnetic resonance spectroscopy in evaluation of cerebral metabolic status before and after carotid endarterectomy/thromboendarterectomy and carotid artery stenting in patients with asymptomatic critical internal carotid artery stenosis. Med Sci Monit 2020; 26: e927029.

[10] Marsman MS, Wetterslev J, Jahrome AK, Gluud C, Moll FL, Keus F and Koning GG. Carotid endarterectomy with patch angioplasty versus primary closure in patients with symptomatic and significant stenosis: a systematic review with meta-analyses and trial sequential analysis of randomized clinical trials. Syst Rev 2021; 10: 139.

[11] Khan JM, McInnis CL, Ross-White A, Day AG, Norman PA and Boyd JG. Overview and diagnostic accuracy of near infrared spectroscopy in carotid endarterectomy: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2021; 62: 695-704.

[12] Zhang Y, Wang W and Fang Q. Clinical study of stent forming for symptomatic internal carotid artery stenosis. Medicine (Baltimore) 2020; 99: e20637.

[13] Ryu B, Ishikawa T, Hashimoto K, Shimizu M, Yagi S, Shimizu T and Kawamata T. Internal carotid artery stenosis with persistent primitive hypoglossal artery treated with carotid artery stenting: a case report and literature review. Neuroradiol J 2016; 29: 115-121.

[14] Chondrogianni M, Lambadiari V, Katsanos AH, Stefanou MI, Palaiodimou L, Triantafyllou AS, Karagiannis G, Konstantakos V, Ioakeimidis M, Triantafyllou S, Zompola C, Liantinioti C, Pappa A, Rizos I, Voumvourakis K, Tsivgoulis G and Boutati E. Omentin is independently associated with stroke severity and ipsilateral carotid artery stenosis in patients with acute cerebral ischemia. J Clin Med 2021; 10: 5797.

[15] Jeong S, Jun JH, Kim JY, Park HJ, Cho YP and Kim GJ. Expression of miRNAs targeting ATP binding cassette transporter 1 (ABCA1) among patients with significant carotid artery stenosis. Biomedicines 2021; 9: 920.

[16] Lin SM, Wang J and Zhou RQ. [Clinical study on treatment of Alzheimer's disease from the viewpoint of Xin and Shen]. Zhongguo Zhong Xi Yi Jie He Za Zhi 2003; 23: 583-586.

[17] Luo T, Cui S, Bian C and Yu X. Crosstalk between TGF-beta/Smad3 and BMP/BMPR2 signaling pathways via miR-17-92 cluster in carotid artery restenosis. Mol Cell Biochem 2014; 389: 169-176.

[18] Gahremanpour A, Perin EC and Silva G. Carotid artery stenting versus endarterectomy: a systematic review. Tex Heart Inst J 2012; 39: 474-487.

[19] Zheng X, Wang Y, Chen G, Ma C, Yan W and Chen M. Diagnosis of ischemic optic neuropathy caused by dissection of the internal carotid artery: a case report. Medicine (Baltimore) 2020; 99: e20034.

[20] Saffari TM, Mathot F, Friedrich PF, Bishop AT and Shin AY. Surgical angiogenesis of decellularized nerve allografts improves early functional recovery in a rat sciatic nerve defect model. Plast Reconstr Surg 2021; 148: 561-570.

[21] Trystula M and Pachalska M. Comorbidities and health-related quality of life following revascularization for asymptomatic critical internal carotid artery stenosis treated with carotid endarterectomy or angioplasty with stenting. Med Sci Monit 2019; 25: 4734-4743.

[22] Li X, Guo D, Hu Y and Chen Y. Oxidative stress and inflammation are associated with coexistent severe multivessel coronary artery stenosis and right carotid artery severe stenosis in elderly patients. Oxid Med Cell Longev 2021; 2021: 2976447.

[23] An L, Chopp M, Zacharek A, Shen Y, Chen Z, Qian Y, Li W, Landschoot-Ward J, Liu Z and Venkat P. Cardiac dysfunction in a mouse vascular dementia model of bilateral common carotid artery stenosis. Front Cardiovasc Med 2021; 8: 681572.