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Comparison of short-term outcomes of patients with embolism-protected and unprotected carotid artery stenting

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ABSTRACT

Objectives: This study aimed to evaluate the effect of using or not using a protective device on clinical outcomes in patients undergoing carotid artery stenting.

Patients and methods: A total of 80 patients (53 males, 27 females; mean age: 68.1±9.1 years; range, 47 to 93 years) with symptomatic severe carotid artery stenosis or asymptomatic severe carotid artery stenosis were included in the prospective study between March 2016 and August 2018. The patients were divided into two groups: those who used an embolism protection device (n=60) and those who did not (n=20).

Results: In terms of primary endpoints, rates of ischemic stroke (5% *vs.* 5%, p=1.00) and transient ischemic attack (5% *vs.* 0%, p=0.56) were found to be similar between the protected and unprotected groups after carotid artery stenting. While total embolism numbers (2.11±2.62 *vs.* 1.26±2.19, p=0.072) and infarct sizes (8.80±4.5 mm *vs.* 9.00±5.05 mm, p=0.97) were similar between the protected and unprotected groups, the presence of silent microemboli was higher in the unprotected group (40% *vs.* 15%, p=0.02).

Conclusion: Although embolism protection devices do not reduce the risk of clinically significant embolism, they significantly reduce the risk of silent microemboli.

Keywords: Carotid artery stenting, embolism protection, microemboli.

In recent years, the use of distal protection devices during carotid artery stenting (CAS) has been the subject of frequent discussion. In the subgroup analysis of the SPACE study, no results were found to support the use of these devices.[1] On the other hand, several studies claim that the results of procedures performed without a distal protection device are excellent.[2-5] In addition to these studies, another important data came from Oteros et al.[6] In their study, 212 high-risk symptomatic patients were stented in the carotid artery without a distal protection device. In 55% of these patients, the severity of the lesion ranged from 90 to 99%, while the severity of the lesion in the remaining patients ranged from 70 to 90%. In this nonrandomized study, the 30-day rate of stroke, death, and myocardial infarction was 1.36%. This rate ranges from 5.2 to 9.6% in large randomized studies comparing endarterectomy and carotid stenting, the majority of which used a distal protection device.[7-9] These results, contrary to expectations, raise the question of whether distal protection devices increase complication rates. Two randomized studies that screened microemboli with diffusion magnetic resonance imaging (MRI) revealed that CAS using an embolism protection device increased the frequency of microemboli in diffusion MRI.[10,11] In light of these conflicting results, this study aimed to compare the use and nonuse of a protective device in patients undergoing CAS.

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PATIENTS AND METHODS

This single-center, prospective study was conducted at the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Department of Cardiology between March 2016 and August 2018. A total of 80 patients (53 males, 27 females; mean age: 68.1±9.1 years; range, 47 to 93 years) with symptomatic severe carotid artery stenosis [angiography ≥50%, ultrasound ≥70%, or computed tomography (CT)/MRI ≥70%] or asymptomatic severe carotid artery stenosis (angiography ≥60%, ultrasound ≥70%, or CT/MRI ≥80%) were included in the study. The patients were divided into two groups: those who used an embolism protection device (n=60) and those who did not (n=20). Those who had a transient ischemic attack, those with amaurosis fugax, those who had a minor or major stroke within six months before the procedure, and those with ischemic defects on cerebral imaging were considered symptomatic. Those who had a major stroke within a week, those with intracranial tumor or arteriovenous malformation, dementia, or severe impairment as a result of stroke, and those with intracranial stenosis were excluded from the study. All patients were started on 100 mg acetylsalicylic acid and 75 mg clopidogrel at least five days before the procedure. This treatment was continued for at least one month after the procedure. Carotid angiography was performed by femoral, brachial, or radial access under local anesthesia with 5F or 6F diagnostic catheters. A Right Judkins coronary catheter or 5F Simmon catheter was used for selective visualization of each of the carotid arteries. Carotid arteries were examined from anteroposterior and lateral poses. The location of the lesion, its length, the degree of stenosis, whether there was compensation from the Willis polygon or the pial arteries, and the presence of anastomosis between the internal and external carotid arteries were evaluated with these angiographies. Open-cell stents were used in all patients. The use of an embolism protection device during the stenting procedure was recorded according to their proximal (EmboShield R; Abbott Vascular, Abbott Park, IL, USA) and distal (Mo. Ma; Medtronic, Minneapolis, MN, USA) locations. Cranial MRI was performed before the CAS procedure. This procedure was repeated after CAS to investigate the presence of new microemboli. Patients who underwent diffusion MRI up to seven days before the procedure were included in the study. Postprocedure diffusion MRI was performed between 24 and 48 h before discharge. In all imaging protocols, diffusion-weighted image sequences were taken to visualize acute and subacute ischemia or infarct. The number and size of the lesions were evaluated by the radiologist.

The CAS procedure was performed under 100 μ/kg unfractionated heparin, and additional heparin was administered when necessary, considering the activated clotting time during the procedure to be 250 to 350 sec. All stent systems, type of embolism protection devices, predilatation, postdilation, use of atropine and anchor technique, telescopic technique, and guiding catheter technique were left to the operator's preference during the CAS procedure. Hemodynamic parameters (e.g., blood pressure, pulse, conscious states, slurred speech, headache, loss of vision, and limitation of extremity movement) were closely monitored for a day in patients who were followed up under coronary intensive care conditions after the CAS procedure. If any neurological signs or symptoms were detected in the patients, their follow-up was completed by asking the opinion of a neurologist urgently.

The primary endpoint of the study was the presence of acute or subacute new ischemic or infarct areas on intrahospital diffusion MRI before discharge, stroke, transient ischemic attack, and myocardial infarction. Stroke was defined as a neurological event lasting ≥24 h. Transient ischemic attack was defined as any neurological event that lasted <24 h. Myocardial infarction was defined as the presence of two of the three criteria: specific cardiac enzymes exceeding two times the upper limit, chest pain that is typical and lasting longer than 30 min, or specific abnormalities on electrocardiography. Technical success was defined as successful stent placement in the carotid artery.

Statistical analysis

Statistical analysis was performed using SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was checked using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) and evaluated using Student's t-test. Categorical variables were presented as number and frequency and assessed using the chi-square. A p-value <0.05 was considered statistically significant.

Table 1
Baseline characteristics of the patients

Variables	Protected group (n=60) n	%	Mean±SD	Unprotected group (n=20) n	%	Mean±SD	*p*
Age (year)			67.8±9.7			69.0±7.2	0.634
Smoking	36	60		8	40		0.097
Diabetes mellitus	23	38.3		6	30		0.502
Sex							
Male	44	78.3		9	45		0.020
Coronary artery disease	39	65		12	60		0.407
Chronic renal failure	5	8.3		3	15		0.405
Hypertension	45	75		15	75		1.00
Hyperlipidemia	14	23.3		9	45		0.064
Chronic heart failure	13	21.7		1	5		0.089
Peripheral artery disease	11	18.3		3	15		1.00
Contralateral carotid stenosis	20	33.3		5	25		0.509
6 months> stroke or TIA	24	40		7	35		0.653

SD: Standard deviation; TIA: Transient ischemic attack; Group 1: Embolism protection device used; Group 2: Embolism protection device not used.

Table 2
Laboratory characteristics of the patients according to groups

Variables	Protected group (n=60) Mean±SD	Unprotected group (n=20) Mean±SD	*p*
Fasting blood glucose (mg/dL)	113.7±27.4	115.2±35.3	0.85
Urea (mg/dL)	41.7±15.5	42.1±17.2	0.95
Creatinine (mg/dL)	1.3±2.4	1.2±0.9	0.86
Sodium (mEq/L)	138.7±3.4	137.6±2.1	0.16
Potassium (mEq/L)	4.3±0.5	4.5±0.4	0.37
AST (IU/L)	19.8±11.1	19.3±9.6	0.85
ALT (IU/L)	19.4±14.1	20.2±11.7	0.83
White blood cell count ($\times 10^9$/L)	4.1±4.5	5.4±3.4	0.21
Neutrophil count ($\times 10^9$/L)	2.5±3.1	3.2±2.2	0.31
Lymphocyte count ($\times 10^9$/L)	1.1±1.3	1.5±1.1	0.07
Hemoglobin (g/dL)	17.1±2.3	13.1±2.1	0.46
Hematocrit (%)	37.4±6.6	39.4±4.9	0.22
Platelet count ($\times 10^9$/L)	127.1±139.1	189.1±126.4	0.08
LVEF (%)	57.5±5.6	56.5±6.9	0.48

SD: Standard deviation; AST: Aspartat transferaz; ALT: Alanin aminotransferaz; LVEF: Left ventricular ejection fraction; Group 1: Embolism protection device used; Group 2: Embolism protection device not used.

Table 3
Procedure-related characteristics of patients

Variables	Protected group (n=60)			Unprotected group (n=20)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Clinically asymptomatic patient	21	35		9	45		0.51
Presence of embolism/infarction before the procedure	54	90		17	85		0.786
Presence of embolism in MRI after the procedure	9	15		8	40		**0.02**
Number of embolisms in MRI after the procedure			2.11±2.62			1.26±2.19	0.072
Embolism size in MRI after the procedure (mm)			8.80±4.5			9.00±5.05	0.979
Mortality (in-hospital)	1	1.7		0	0		0.744
Myocardial infarction (in-hospital)	0	0		0	0		1.00
Intracranial hemorrhage (in-hospital)	0	0		0	0		1.00
Stroke (in-hospital)	3	5		1	5		1.00
Transient ischemic attack	3	5		0	0		0.56
Procedural site complication	5	8.3		0	0		0.32
Hyperperfusion syndrome	0	0		1	5		0.25
Hypotension during the procedure	12	20		1	5		0.167
Bradycardia/atropine during the procedure	14	23.3		0	0		**0.016**
Hypertension during the procedure	0	0		1	5		0.25

SD: Standard deviation; MRI: Magnetic resonance imaging; Group 1: Embolism protection device used; Group 2: Embolism protection device not used.

RESULTS

In the protective device group, a distal protection device was used in 55 patients, and a proximal protection device was used in five patients. Bilateral carotid stenosis was present in 25 (31.2%) of the patients. Thirty-one (38.7%) of the patients had a history of ischemic stroke or transient ischemic attack before six months. There was no significant difference in baseline characteristics between embolism-protected and unprotected groups, except for sex (Table 1). More males were present in the protected group (p=0.02). The mean left ventricular ejection fraction of the patients was 57.25±5.9%. There was no significant difference between the laboratory findings of the groups (Table 2). Thirty (37.5%) of the patients who underwent CAS were clinically asymptomatic. Sixty-one (76.2%) of the patients had infarct findings in the MRI performed before the procedure. In-hospital mortality developed in one (1.25%) patient after the procedure. Considering the primary endpoints, the rates of ischemic stroke (5% *vs.* 5%, p=1.00) and transient ischemic attack (5% *vs.* 0%, p=0.56) were found to be similar between the protected and unprotected groups after the CAS procedure. While total emboli numbers (2.11±2.62 *vs.* 1.26±2.19, p=0.072) and infarct sizes (8.80±4.5 mm *vs.* 9.00±5.05 mm, p=0.97) were similar between the protected and unprotected groups, the presence of silent microemboli was higher in the unprotected group (40% *vs.* 15%, p=0.02). Bradycardia and atropine requirement during the procedure was significantly higher in the group using a protective device (23.3% *vs.* 0%, p=0.016, Table 3).

DISCUSSION

Cerebral protection devices were started to be used with the assumption that they would prevent cerebral embolism during carotid stent placement. Case reviews compared old unprotected data with newly protected data.[11,12] However, this mostly reflects advances in technique and patient selection. New studies reveal that cerebral protection devices have no effect on death, stroke, and myocardial infarction in the first 30 days, contrary to today's general use.[13,14] In another study, it was found that the use of a protective device led to new ischemic lesions revealed by diffusion MRI after

the procedure.[14] Contrary to these studies, in the first 80 patients of the EVA-3 (Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis) study, stroke was detected four times more frequently in unprotected CAS, and the study was interrupted.[15] However, this difference is unlikely to be explained by the use of a protection device since only two of the patients who did not use a filter had a stroke on the day of the procedure. In our study, although it was not statistically significant, stroke or transient ischemic attack developed in six patients in whom protection was used, while it occurred in only one case in which protection was not used.

The 2017 European Society of Cardiology guideline raised the use of protective devices to class 2A.[16] However, the studies used justified to this change are old and not multicenter, randomized studies. Two small randomized studies have shown that microemboli protection devices increase microemboli.[6-11,17] In our study, microemboli were more common in the unprotected group in postprocedure MRI (p=0.020). However, our study was not a randomized study, and the unprotected group consisted of more difficult cases where the use of filters was not possible. More ischemic foci were detected in the MRI images before the procedure in the unprotected group. However, the number of clinically significant events after the procedure was higher in the protected group. In addition, bradycardia and atropine requirement during the procedure were higher in the group using the protective device. The reason for this was thought to be the increased stimulation of the carotid bulb due to manipulation of the protection device. This is an important problem of the CAS process and adversely affects the results.

The main limitation of the study is that it was not a randomized controlled trial. Another limitation is the lack of statistical significance in the primary endpoints due to the relatively small number of patients.

In conclusion, the present study showed that cerebral protection devices used in carotid stenting did not reduce the risk of clinically reflected cerebral embolism but significantly reduced the risk of silent microemboli.

Ethics Committee Approval: The study protocol was approved by the Acibadem University Medical Research Evaluation Board (date: 31.03.2016, no: 2016-5/8). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conception and design of the study, data collection and drafting of manuscript: Y.D., A.D.; Analysis and interpretation of data: O.Ş.; Acquisition of data and critical revision: A.E.

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