RESEARCH LETTER

Cerebral ischemic lesions on diffusion-weighted magnetic resonance imaging after carotid eversion endarterectomy vs carotid stenting with a proximal protection device: results of a randomized prospective trial

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Introduction Periprocedural cerebral microembolism associated with carotid artery revascularization does not usually manifest as a clinically overt stroke. Such microembolism can result in cognitive impairment, which is difficult to measure objectively. Yet, neuropsychological disturbances resulting from these events represent an important clinical and socioeconomic problem.[1,2] Theoretically, proximal protection, because of flow reversal during endovascular repair,[3-10] should be associated with a decreased risk of periprocedural microembolism when compared with surgical endarterectomy. In this trial, we demonstrated that there were indeed fewer microembolic cerebral ischemic lesions after stenting with a proximal protection device compared with surgical eversion endarterectomy, which—if proven by a larger study—would be of particular clinical significance.

Methods CARECarotid (New Ischemic Cerebral Lesions After Endarterectomy vs. Stenting for the Treatment of Symptomatic Carotid Stenosis) was a prospective randomized single-center study, performed at the University Hospital in Kraków, Poland. The study protocol was approved by the Bioethical Committee of the Regional Board of Physicians in Kraków (approval no., 137/KBL/OIL/2015) and was registered at ClinicalTrials.gov (identifier, NCT03764306). It was planned to evaluate 50 patients presenting with symptomatic lesions of the internal carotid artery.

The inclusion criteria were as follows: age ≥18 years; 60%–99% stenosis of the internal carotid artery; diameter of the target internal carotid artery ≤7 mm; symptomatic lesion (history of ipsilateral stroke, transient ischemic attack, or reversible ischemic neurological deficit); localization and morphology of the lesion enabling surgical eversion endarterectomy or endovascular angioplasty with stenting; and written informed consent.

The exclusion criteria comprised a target lesion that has been previously stented or operated; highly calcified lesions; occlusion of the contralateral carotid artery without adequate collateral circulation through the circle of Willis; anatomical contraindications for eversion endarterectomy; acute ipsilateral stroke; disabling stroke at any side; other severe pathologies of the brain, resulting in a significant loss of cerebral tissue and/or significant neurological deficits; history of hemorrhagic transformation of ischemic stroke; severe comorbidities; allergy to aspirin, clopidogrel, or ticlopidine; allergy to iodinated contrast media; pregnancy; and metallic implants or other known contraindications to magnetic resonance imaging. Women of reproductive age who did not use effective contraception were also excluded.

It was a randomized study with parallel groups. We used closed envelopes as a randomization tool. Patients were randomly assigned to one of the 2 treatment arms: surgical endarterectomy or carotid angioplasty with stenting under proximal protection. All patients provided written informed consent to undergo procedures and to participate in this trial.

The study was conducted from May 2015 to March 2018. During this time, a total of 214 patients in our center underwent either surgical (41 patients) or endovascular treatment (173 patients) for carotid artery stenosis. However, only 31 patients met the inclusion and exclusion criteria of this trial. Due to problems with recruitment and also with financing interventional and diagnostic procedures, we terminated the study before the target number of 50 patients had been reached.

Study endpoints The primary endpoint of this study was the proportion of patients who had new cerebral lesions on magnetic resonance imaging 2 to 3 days after the procedure.

Study definitions Patients were considered symptomatic if they had an ipsilateral neurological ischemic event during 60 days before the planned procedure. An ischemic lesion was considered ipsilateral if it occurred in cerebral tissue supplied by the target carotid artery. Surgical endarterectomy was considered successful if there was no residual stenosis after the procedure. Endovascular angioplasty with stenting was considered successful if there was no residual stenosis greater than 20% and there was no dissection of the target artery following the procedure.

Patients After randomization, 14 patients were assigned to the surgical arm, and 17 patients, to the stent arm. The mean (SD) age of patients was 69 (7.7) years: 70.1 (7.7) years in the surgical arm and 68.1 (7.7) years in the stent arm. There were no significant differences between the study arms regarding age and sex of patients or lateralization of the lesions. The mean (SD) length of the target lesion was 14.5 (2.5) mm in the surgical arm and 14.9 (5.9) mm in the stent arm. The mean (SD) degree of stenosis, assessed by Doppler sonography, computed tomography angiography, or catheter angiography, was 83.2% (5.7%) in the surgical arm and 91.2% (10.8%) in the stent arm. These differences were nonsignificant.

There were no significant differences between the groups regarding comorbidities. The median time from symptoms to the procedure was 10 days in the stent arm and 12 days in the surgical arm. This difference was also nonsignificant and was probably associated with a more complex preparation of patients for surgical treatment. In the surgical arm, the National Institutes of Health Stroke Scale (NIHSS) scores varied from 0 to 5. The mean (SD) NIHSS score was 1.1 (1.8); thus, the neurological status ranged from no stroke to symptoms of moderate stroke. Similarly, in the stent arm, these scores varied from 0 to 5, with the mean (SD) score of 2 (1.18). The difference in the NIHSS score between the study arms was not significant.

In all surgical patients, carotid endarterectomy was performed using the eversion technique and cervical block anesthesia. Shunt was used only in 1 patient, as the other patients presented with adequate collateral circulation. All surgical endarterectomies fully restored blood flow through the target carotid artery. There were no perioperative complications in the surgical arm, except for 1 patient who required urgent angioplasty and stent implantation due to dissection of the target artery, which was localized distally to the site of endarterectomy. Endovascular treatment restored proper flow and there were no further complications in this patient.

All procedures in the stent arm were performed using the Mo.Ma proximal cerebral protection device (Medtronic, Minneapolis, Minnesota, United States). We implanted stents that were tailored to the localization of the lesions and morphology of the carotid arteries. In the case of rather straight arteries, we used Carotid Wallstent stents (Boston Scientific, Massachusetts, United States), while in patients with tortuous arteries, we implanted Precise Pro RX stents (Cordis, Fremont, California, United States) or Roadsaver stents (Terumo, Tokyo, Japan). Carotid Wallstent stents were used in 10 patients; Roadsaver, in 5 patients; and Precise Pro RX, in 2 patients. There were no technical failures associated with stent implantations.

Magnetic resonance imaging Diffusion-weighted magnetic resonance sequences of the brain were acquired using a GE 3 Tesla HDx magnetic resonance scanner (GE Healthcare, Chicago, Illinois, United States). In both arms of the trial, the imaging was performed 1 to 3 days before the procedure and 2 to 3 days after revascularization. The following sequences were acquired: standard T1 and T2, axial diffusion-weighted imaging, 3-dimensional time-of-flight, and the enhanced susceptibility-weighted angiography. The images were interpreted by a neuroradiologist who was blinded to the procedures. In order to secure the blinding, he did not see patients during imaging. Also, in order not to reveal stents, magnetic resonance scans did not cover the patients' necks.

Statistical analysis Categorical variables were compared between the groups the χ^2 test or the extended Mantel–Haenszel χ^2 for linear trend test. Continuous variables were compared using the independent sample t test or, in the case of nonnormal distribution, the Mann–Whitney test. The significance of the tests was set at a P value of less than 0.05.

Results Diffusion-weighted magnetic resonance imaging before surgical endarterectomy

TABLE 1 Results of diffusion-weighted magnetic resonance imaging after carotid eversion endarterectomy (surgical arm) and carotid stenting (stent arm)

Characteristics on DW-MRI	Surgical arm (n = 14)	Stent arm (n = 17)	*P* value
Patients with new ischemic lesions, n (%)	7 (50.0)	6 (35.3)	NS
Patients with new ipsilateral ischemic lesions, n (%)	5 (35.7)	4 (23.5)	NS
Patients with new contralateral ischemic lesions, n (%)	2 (14.3)	2 (11.8)	NS
Patients with new ipsilateral lesions smaller than 1 cm, n (%)	1 (7.1)	4 (23.5)	NS
Patients with new ipsilateral lesions larger than 1 cm, n (%)	4 (28.6)	0	0.02
Total number of new lesions	62	16	NS
Number of new lesions in patients presenting with such lesions, mean (range)	8.9 (1–22)	2.7 (1–6)	NS
Total number of new ipsilateral lesions	57	14	NS
Total number of new ipsilateral lesions smaller than 1 cm	45	14	NS
Total number of new ipsilateral lesions larger than 1 cm	12	0	0.02
Total number of new contralateral lesions	5	2	NS

Abbreviations: DW, diffusion-weighted magnetic resonance imaging; NS, nonsignificant

or stenting revealed no significant differences regarding cerebral atrophy, leukoaraiosis, or foci of cerebral microinfarction. There was a trend towards more new posttreatment ischemic lesions in the surgical arm in comparison with the stent arm (50% vs 35.3% for all patients with new ischemic lesions, and 35.7% vs 23.5% for ipsilateral lesions), but the differences were not significant. Yet, ipsilateral lesions larger than 1 cm in diameter were revealed only in the surgical arm, and this finding was significant. These lesions were differently localized within the brain but all were found in the cerebral territory supplied by the anterior and / or middle cerebral arteries, and their macroscopic characteristics were suggestive of microembolism.

The mean number of new ischemic lesions revealed by postprocedural magnetic resonance imaging was higher in the surgical arm (8.9 vs 2.7), but the difference was not significant. Importantly, all new ischemic lesions found in patients managed with stents were smaller than 1 cm in diameter. There were no significant differences between the incidence of contralaterally localized lesions. Details are presented in **TABLE 1**.

Discussion This prospective randomized trial demonstrated that there were fewer new large ischemic lesions after endovascular angioplasty with stenting with a proximal protection device in comparison with surgical eversion endarterectomy. However, there are some important limitations of our study. This was a single-center study with a small sample size. Because of the problems with recruitment and financing, we were forced to terminate the study prematurely. Consequently, a trend could be demonstrated for some variables, however without statistical significance. Perhaps significance regarding small postprocedural ischemic lesions could be confirmed in a larger cohort.

It is known that the eversion technique is associated with less frequent perioperative microembolic events when compared with standard endarterectomy.[11] Nonetheless, a majority of microemboli is probably released during dissection of the carotid arteries. Novel surgical methods focus on no-touch isolation technique for these arteries.[12] Perhaps in future studies assessing the risk of postprocedural cerebral microembolism, patients should be managed using such a no-touch surgical technique.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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