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More new ischemic cerebral lesions revealed by diffusion-weighted imaging magnetic resonance imaging after carotid eversion endarterectomy in comparison with carotid stenting under proximal protection: the results of randomized prospective trial

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**Short running title:** New ischemic cerebral lesions after CEA vs. CAS

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Periprocedural cerebral microembolism associated with carotid artery revascularization does not usually manifest as 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, a proximal protection, because of the reversal of flow during endovascular repair [3-10], should be associated with decreased risk of periprocedural microembolism if compared to surgical endarterectomy. In this trial we have demonstrated that there were indeed fewer microembolic cerebral ischemic lesions after stenting under proximal protection in comparison with surgical eversion endarterectomy, which—if proven by a larger study—would be of particular clinical significance.

Methods

The CARE Carotid (Endarterectomy vs. Angioplasty with proximal protection system in patients with symptomatic lesions of the internal Carotid artery) was a prospective randomized single-centre study, which was performed in the University Hospital in Kraków. Study protocol has been approved by the Bioethical Committee of the Regional Board of Physicians in Kraków (approval 137/KBL/OIL/2015) and has been registered at ClinicalTrials.gov; identifier: NCT03764306. It was planned to evaluate 50 patients presenting with symptomatic lesions of the internal carotid artery.

Inclusion criteria comprised:

- patient’s age ≥18 years;
- 60-99% stenosis of the internal carotid artery;
- diameter of 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 making possible surgical eversion endarterectomy or endovascular angioplasty with stenting;

• written informed consent.

Exclusion criteria comprised:

• target lesion that has been previously stented or operated;

• highly calcified lesions;

• occlusion of 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 significant loss of cerebral tissue and/or significant neurological deficits;

• history of hemorrhagic transformation of ischemic stroke;

• severe co-morbidities;

• allergy to aspirin, clopidogrel or ticlopidine;

• allergy to iodinated contrast media;

• pregnancy;

• women of reproductive age who do not use effective contraception;

• metallic implants or other known contraindications for magnetic resonance imaging.
It was a randomization study with parallel groups. We used closed envelopes as a randomization tool. Patients were randomly assigned to one of the two treatment arms: surgical endarterectomy or carotid angioplasty with stenting under proximal protection. All patients provided their written informed consent to undergo procedures and to participate in this trial.

Study was conducted from May 2015 to March 2018. During this time in our centre a total of 214 patients underwent either surgical (41 patients) or endovascular treatment (173 patients) for carotid artery stenosis. Still, only 31 patients met 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 has been reached.

*Study endpoints*

The primary endpoint of this study was the proportion of patients who had new cerebral lesions revealed by magnetic resonance imaging 2-3 days after the procedure.

*Study definitions*

Patients were considered symptomatic if they had an ipsilateral neurological ischemic event during 60 days before planned procedure. 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 procedure. Endovascular angioplasty with stenting was considered successful if there was no residual stenosis greater than 20% and there was no dissection of 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 69.0 years; 70.1 (7.7) in surgical arm and 68.1 (7.7) in stent arm. There were no statistically significant differences between arms of the study regarding age and sex of patients, and lateralization of the lesions. The mean (SD) length of target lesion was 14.5 (2.5) mm in surgical arm and 14.9 (5.9) mm in stent arm. Mean (SD) degree of stenosis, which was assessed by means of Doppler sonography, CT 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 statistically insignificant.

There were no significant differences between the groups regarding patients’ comorbidities.

Median time from symptoms to the procedure was 10 days in the stent arm and 12 days in surgical arm. This difference was not statistically significant and was probably associated with more complex preparation of patients to surgical treatment. In the surgical arm the National Institutes of Health Stroke Scale (NIHS) scores varied from 0 to 5; mean (SD) NIHS score was 1.1 (1.8), thus from no stroke to symptoms of a moderate stroke. Similarly, in the stent arm these scores varied from 0 to 5; mean (SD) score was 2 (1.18). Difference between study arms regarding NIHS scores was not statistically significant.

In all surgical patients carotid endarterectomy was performed using eversion technique and under cervical block anesthesia. Shunt was used only in 1 patient, other patients presented with adequate collateral circulation and the use of shunt was not required. All surgical endarterectomies fully restored blood flow through target carotid artery. There were no perioperative complications in the surgical arm, except for one patient who required urgent angioplasty and stent implantation due to dissection of the target artery, which was localized.
distally from the area of endarterectomy. Endovascular treatment restored proper flow and there were no further complications in this patient.

All procedures in the stent arm were performed under proximal protection, with the use of Mo.Ma (Medtronic, Minneapolis, MN, USA) device. We implanted stents that were tailored to the localization of lesions and morphology of carotid arteries. In a case of rather straight arteries we utilized Carotid Wallstent (Boston Scientific, Natick, MA, USA) stents, in patients with tortuous arteries we implanted Precise Pro RX (Cordis, Fremont, CA, USA) or Roadsaver (Terumo, Tokyo, Japan) stents. In 10 patients we implanted Carotid Wallstent stents, in 5 patients Roadsaver stents, and in 2 patients Precise Pro RX stents. 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. In both arms of the trial the imaging was performed 1-3 days before procedure and 2-3 days after revascularization. The following sequences were acquired: standard T1 and T2, axial diffusion-weighted imaging (DWI), 3D time-of-flight (TOF), and the enhanced susceptibility-weighted angiography (ESWAN). Interpretation of the images was done by the neuroradiologist who was blinded to the procedures. In order to secure the blinding, he did not see patients during imaging. Also, in order to not reveal stents, MR scans did not cover patients’ necks.

*Statistical analysis*
Comparison of categorical variables between the groups was performed using the chi-square test or the extended Mantel-Haenszel chi-square for linear trend test. Comparisons of continuous variables were performed using the independent sample t-test or, in a case of non-normal distribution, the Mann-Whitney U test. The significance of the tests was set at $p < 0.05$.

Results

There were no statistically significant differences regarding cerebral atrophy, leukoaraiosis or foci of cerebral microinfarction revealed by the diffusion-weighted magnetic resonance imaging before surgical endarterectomy or stenting. There was a trend towards more new post-treatment ischaemic lesions in the surgical arm in comparison with the stent arm (50.0% vs. 35.3% regarding all patients with new ischemic lesions; and 35.7% vs. 23.5% regarding ipsilateral lesions) but these differences were not statistically significant. Yet, ipsilateral lesions larger than 1 cm in diameter were revealed only in the surgical arm and this phenomenon was statistically 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.

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

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

Moreover, it is known that the eversion technique is associated with less frequent perioperative microembolic events when compared to standard endarterectomy [11]. Nonetheless, a majority of microemboli is probably released during dissection of carotid arteries. Novel surgical techniques focus at non-touch isolation of these arteries [12]. Perhaps in future studies assessing the risk of postprocedural cerebral microembolism patients should be managed using such a non-touch surgical technique.

References:


Table 1. Diffusion-Weighted Magnetic Resonance Imaging after procedures.

<table>
<thead>
<tr>
<th></th>
<th>Surgical arm (N=14)</th>
<th>Stent arm (N=17)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with new ischemic lesions</td>
<td>7 (50.0%)</td>
<td>6 (35.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with new ipsilateral ischemic lesions</td>
<td>5 (35.7%)</td>
<td>4 (23.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with new contralateral ischemic lesions</td>
<td>2 (14.3%)</td>
<td>2 (11.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with new ipsilateral lesions smaller than 1 cm</td>
<td>1 (7.1%)</td>
<td>4 (23.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with new ipsilateral lesions larger than 1 cm</td>
<td>4 (28.6%)</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Total number of new lesions</td>
<td>62</td>
<td>16</td>
<td>NS</td>
</tr>
<tr>
<td>Number of new lesions in patients presenting with such lesions (mean; range)</td>
<td>8.9 (1-22)</td>
<td>2.7 (1-6)</td>
<td>NS</td>
</tr>
<tr>
<td>Total number of new ipsilateral lesions</td>
<td>57</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Total number of new ipsilateral lesions smaller than 1 cm</td>
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<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Total number of new ipsilateral lesions larger than 1 cm</td>
<td>12</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Total number of new contralateral lesions</td>
<td>5</td>
<td>2</td>
<td>NS</td>
</tr>
</tbody>
</table>