

Neural Damage Biomarkers during Open Carotid Surgery versus Endovascular Approach[☆]

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Background: Carotid endarterectomy (CEA) is the gold standard for treating severe carotid artery stenosis, whereas carotid artery stenting (CAS) represents an endovascular alternative. The objective of this study was to assess the potential neural damage following open or endovascular carotid surgery measured by peripheral blood concentration of 3 biomarkers: S100 β , matrix metalloproteinase-9 (MMP-9), and D-dimer.

Methods: Data for this prospective investigation were obtained from the Carotid Markers study (January 2010–2011), which sought to measure the levels of specific biomarkers of neuronal damage and thrombosis on candidates to CEA or CAS presenting at the Department of Vascular Surgery of the Nuovo Ospedale S. Agostino Estense of Modena (Italy) at baseline and at 24 hr after surgery. Relevant medical comorbidities were noted.

Results: A total of 113 consecutive patients were enrolled in the study, 41 in the endarterectomy group and 72 in the endovascular group. The baseline levels of the studied biomarkers did not show any statistically significant difference between the groups with the exception of MMP-9, which showed higher concentrations in the endovascular group (median 731 vs. 401, $P = 0.0007$), while 24 hr after surgery the endarterectomy group featured significantly higher peripheral blood concentrations of MMP-9, S100 β , and D-dimer. Conversely, no significant difference was detected in the endovascular group except the D-dimer level.

Conclusions: Neural damage biomarkers demonstrated a substantial difference between open and endovascular carotid surgery, which, if performed in selected patients, may become a less invasive alternative to CEA.

INTRODUCTION

Stroke is one of the leading causes of death and permanent disability in high-income countries.¹ Significant carotid artery stenosis may be a predisposing factor in stroke, so surgical treatment can reduce

the risk of recurrent stroke in patients with severe carotid stenosis.²

Carotid endarterectomy (CEA) is the gold standard for treating severe carotid artery stenosis, whereas carotid artery stenting (CAS) represents its endovascular alternative.^{3,4} Open surgery has

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The study was funded with institutional funds for independent research of the University of Modena and Reggio Emilia.

Disclosures: Prof. Gioachino Coppi is the patent holder of Mo.Ma[®] and Pilon GC[®]. Dr. Roberto Moratto and Dr. Jessica Veronesi work at the Department of Vascular Surgery of the Nuovo Ospedale S. Agostino Estense Modena, Italy under the direction of prof. Gioachino Coppi.

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Ann Vasc Surg 2014; 28: 1671–1679

<http://dx.doi.org/10.1016/j.avsg.2014.05.006>

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Manuscript received: December 22, 2013; manuscript accepted: May 30, 2014; published online: June 6, 2014.

demonstrated, on one hand, a lower periprocedural risk of death and stroke, with, on the other hand, a higher risk of acute myocardial infarction (AMI) and cranial nerve injury, making percutaneous transluminal angioplasty and CAS second-line treatment options for carotid artery stenosis. However, no long-term differences concerning the outcome of stroke or death were demonstrated in the meta-analysis by Meier et al.⁵

This meta-analysis and several trials, Carotid Revascularization Endarterectomy versus Stenting Trial (CREST),^{6,7} Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS),⁸ and Steant-Protected Angioplasty versus Carotid Endarterectomy (SPACE),⁹ have shifted the balance in favor of CEA,¹⁰ because of the lower incidence of cerebrovascular complications,¹¹ reserving endovascular techniques to selected cases.

The diagnosis of periprocedural stroke relies on clinical parameters and neuroimaging techniques,¹² as with all other forms of acute stroke. Similarly to what has been done for early triage and evaluation of cardiac symptoms compatible with AMI, various panels of biomarkers of neural damage^{13–15} have been developed and validated in recent years. The necessity of adopting a multiple markers approach is based on the absence of a single molecule capable of identifying brain damage in all its forms. S100 β ,¹⁶ a calcium-binding protein, is released from astrocytes—a cellular population that is vital to neuronal trophic support being involved in most repair and apoptosis processes. Matrix metalloproteinase-9 (MMP-9),^{17,18} a gelatinase, is less neuron specific as it is a marker of inflammation, present in both active and inactive forms, the former being more abundant within the blood–brain barrier indicating, at high concentration, damage at this level. D-dimer¹⁹ is the end product of fibrinolytic process. These 3 markers are part of the triage stroke panel,¹³ the brain natriuretic peptide, present in the original version, was excluded from the perioperative assays as it could be biased by surgery-related variables not correlated to neural damage, such as fluid therapy and cardiac function.

A biomarker-based approach can be proposed to assess potential periprocedural neurological damage whose effects are still present at 24 hr; this could help to identify more subtle variations and uncover subclinical, active injuries that might contribute to the development of long-term effects. In fact, an acute elevation of these biomarkers could result solely from minor surgical alterations to cerebral perfusion and inflammation, while a lasting elevation at 24 hr may be correlated to a more substantial lesion.

The main objective of this investigation was to assess the potential neural damage following open versus endovascular carotid surgery measured by peripheral blood concentration of 3 biomarkers (S100 β , MMP-9, D-dimer) at baseline and 24 hr after surgery.

METHODS

Data for this prospective pilot investigation were obtained from the Carotid Markers (CARMA) study (January 2010–2011), which sought to measure the levels of specific biomarkers of neuronal damage and thrombosis on candidates to CEA or CAS presenting at the Department of Vascular Surgery of the Nuovo Ospedale S. Agostino Estense (Baggiovara, Modena, Italy) at baseline and at 24 hr after surgery. Approval from Institutional Ethics Committee of Modena was obtained before study initiation. Patients were included in the analysis if CEA or CAS were performed according to the below described techniques. Written formal consent was obtained from the study participants or legal designate. Demographic, clinical, laboratory, and radiographic data were collected by a standardized protocol. The American Society of Anesthesiologists (ASA) physical status classification system was adopted as a measure of the overall physical health of the patient before surgery.

Initial assessment of the patient was performed by echo-color duplex scan and angio-computed tomography (CT) of the neck and brain to define the anatomical characteristics of the aortic arch, supra-aortic vessels, and intracranial circulation. Asymptomatic patients with stenosis >80% and/or ulcerated lesions >50% and symptomatic patients with stenosis >60% and/or ulcerated lesions >50% were considered for treatment. Patients over 65 years of age were primarily considered for CAS at this center when favorable anatomies were documented at angio-CT studies. Suitable anatomic criteria for CAS included bovine and normal arches (type I, II, and III) and adequate femoral artery access. Endovascular treatment was withheld in cases of stenosis of the brachiocephalic artery or at the origin of the left common carotid artery (CCA) and calcification of the aortic arch. Patients were considered for CAS when unsuitable for traditional surgery because of clinically significant cardiac disease, severe pulmonary disease, contralateral laryngeal nerve palsy, restenosis >80% after CEA, previous neck radiation exposure or radical neck surgery, and high carotid bifurcation or intracranial extension of a carotid lesion. Finally, CAS was performed in patients at high risk of cerebral ischemia during carotid clamping (i.e., occlusion of the

contralateral internal carotid artery (ICA) and anomalies of the circle of Willis). There is no maximum age threshold at this center, but patients aged under 65 years, who were suitable for surgery, were preferably treated with CEA.

All new neurological deficits, defined as previously not documented focal or general neurological signs or symptoms presented by the patient during and after surgery were recorded by a consultant neurologist.

Surgical Techniques

Carotid endarterectomy. The eversion CEA technique was performed through an oblique transection of the ICA from the CCA, endarterectomy by eversion of the ICA, endarterectomy of the carotid bifurcation and of the external carotid artery (ECA), and reimplantation of the ICA on the CCA. Conventional CEA was performed through a longitudinal arteriotomy from the CCA bifurcation to the ICA on the anterior surface of the artery. Endarterectomy was carried out after careful identification of the cleavage plane. Arteriotomy was routinely closed with a prosthetic patch (Finesse Fine, Maquet, NJ).

The procedure was performed during conscious sedation: after the cannulation of a peripheral vein with a large bore catheter and radial artery with a 20G catheter for invasive monitoring of blood pressure, general anesthesia was induced using propofol 1% (1–1.5 mg/kg) and remifentanyl continuous infusion at a rate of 0.1–0.15 µg/kg/min. All patients received succinylcholine 1 mg/kg before laryngoscopy and topical lidocaine 4% on the vocal cords before intubation. After the endotracheal tube was positioned, mechanical ventilation started. The superficial cervical plexus block was performed using ropivacaine 0.75% (0.8–1.2 mg/kg). Under remifentanyl continuous infusion at a rate of 0.1 µg/kg/min, the patient regained consciousness with the ability to tolerate orotracheal intubation and mechanically assisted ventilation; no other anesthetic agent was administered alongside remifentanyl. Cerebral blood flow adequacy, after carotid clamping, was measured by monitoring the ability of the patient to execute simple orders (squeeze test) issued by the anesthesiologist at regular intervals, of at least 5 min or more frequently if necessary, with the hemisoma contralateral to the surgical site: inability to perform this task, in the absence of other possible causes such as systemic hypotension, was the indication for carotid shunt placement.

The remifentanyl infusion was gradually reduced and completely discontinued at the end of the procedure and the patient was extubated.

The anesthesia protocol used combines a regional technique with conscious sedation to ensure adequate pain control and safe airway management.

Carotid artery stenting. An access was obtained by percutaneous puncture of the common femoral artery under local anesthesia with mepivacaine 5 mg/kg. The Piton GC[®] carotid guide catheter (Medtronic Invatec, Frauenfeld, Switzerland) and Mo.Ma[®],^{20,21} a proximal cerebral embolic protection device, (Medtronic Invatec) were used in all cases. Predilation was selectively performed with a noncompliant coronary balloon (2.5–3.5 mm in diameter) in case of preocclusive calcified stenosis (a stenosis of at least 90%) which impeded stent deployment. Self-expanding nitinol stents were used in the study. The diameter of the stent was chosen according to a 1–2 mm oversizing with a length of 30 or 40 mm. In the case of lesions longer than 40 mm, 2 stents were inserted, with an overlapping of 2–5 mm. Double stenting was employed for longer lesions and not for stent design reinforcement (in 1 case double stenting was employed to avoid plaque prolapse). Stents used in this study include X-act[®] (Abbott Vascular, Redwood City, CA), ViVEXX[®] (C. R. Bard, Murray Hill, NJ), VascuFlex[®] (B. Braun Medical, Boulogne Cedex, France), and Cristallo Ideale Carotid Stent System[®] (Medtronic Invatec). Postdilation was performed with a 5 × 20 mm noncompliant balloon (range 4–5.5 mm) at 8 atm, with inflation and deflation performed slowly (1 atm/2 sec). After the final aspiration, when there were no signs of clamping intolerance, endovascular flushing to the ECA was performed. Before the removal of the protection device, the postdilation balloon was reintroduced into the ICA and reinflating at a low pressure (4 atm) to further remodel the debris or detached protruding plaque. The balloons in the ECA and CCA were then deflated, allowing passage of the reinstated hematic current into the ECA for 5–10 sec (cerebral flow is blocked by the inflated postdilation balloon). Then balloons were reinflated and the postdilation balloon was deflated and removed. A second aspiration was performed, checking for the absence of debris before reinstating blood flow and removing the device. This procedure was intended to mobilize the unstable protruding plaque while the cerebral flow was still blocked and redirect it into the ECA, achieving a spreading effect of any protruding plaque. An intra- and extracranial angiography post intervention was performed to assess stent patency and eventual residual stenosis (≤20% is accepted)

and to visualize and assess any potential intracranial embolization.

The choice of the stent used was based on both anatomical and plaque-related criteria: closed cells were preferred in linear vessels with soft plaques, open cells in cases of tortuous anatomies with calcified plaques, while hybrid cells were used in soft plaques.

Postoperative Medical Therapy

All candidates to CAS received aspirin 100 mg and clopidogrel 75 mg daily for the 3 days preceding the operation. During both procedures a standard dose of heparin was administered and from the first postoperative day an antiplatelet regimen with aspirin 100 mg, associated for 30 days to clopidogrel in case of CAS. Statins were added as plaque stabilizers, when not absolutely contraindicated.

Immunoassays

Blood samples were obtained at admission to the Department of Vascular Surgery and after 24 hr by either venous puncture or a catheter placed in the radial artery for the invasive monitoring of blood pressure. Plasma samples were collected in ethylenediaminetetraacetic acid tubes for D-dimer; serum samples were collected for S100 β and MMP-9 detection. Blood samples were centrifuged at $1,500 \times g$ within 60 min from collection. Each serum or plasma sample was subdivided into 2 Cryo-Vials™ and stored at -80°C .

Serum MMP-9 was quantified by a commercially available MMP-9 (human) ELISA kit (DRG Diagnostics, DRG Instruments GmbH, Marburg, Germany). Serum S100 β was quantified with appropriate fully automated electrochemiluminescence immunoassay (Cobas; Roche Diagnostics GmbH, Mannheim, Germany) in accordance with the manufacturer's instructions. Plasma D-dimer concentration was measured using a fully automated Tina-quant D-dimer D-DI2 test (Cobas; Roche Diagnostics GmbH) according to the manufacturer's instructions. The lower limit of sensitivity of the MMP-9 assay was 0.05 ng/mL, while the analytic range for D-dimer and S100 β was 150–9,000 ng/mL and 0.005–39 $\mu\text{g/L}$, respectively.

Follow-up

All included patients were scheduled for follow-up 1 week after the procedure, 1 and 6 months afterwards: on these occasions a carotid ultrasound scan was acquired by a vascular surgeon, who also evaluated potential surgical complications, while a neurologist performed a detailed neurological

examination to detect potential lesions correlated to surgery and follow their evolution.

Statistical Analysis

Statistical analysis was performed using Stata 10.0 (StataCorp, College Station, TX). Descriptive statistics, including median and interquartile range, were obtained for demographic variables, Wilcoxon rank-sum test was used to compare the distributions of continuous variables, the Wilcoxon sign-rank test for paired data, and χ^2 test for categorical variables. The Spearman's rank correlation test was used to assess the relationship between 2 interval variables.

RESULTS

A total of 113 consecutive patients were enrolled in the CARMA study, 41 in the endarterectomy group and 72 in the endovascular group. Figure 1 reports the enrollment flowchart: 82.9% of the subjects in the endarterectomy group were treated with patch angioplasty and 17.1% with eversion.

The demographics for the study population did not show statistically significant differences between groups as regard to sex, vascular risk factors, and relevant past medical history, with the exception of age and peripheral artery disease (PAD) (Table I); the median degree of preoperative carotid stenosis, measured by echo-color duplex scan as percentage of lumen reduction in the vessel to be operated, was 75% in both groups ($P = 0.1961$). No deaths were reported during hospital stay and 2 patients died during the follow-up period (1.6%): one for the complications of a stroke at day 24 in the endovascular group and one after a cerebral hemorrhage at day 150 in the endarterectomy group.

The mean duration of the perioperative period of the endarterectomy group was 95.8 ± 9.0 min, while for CAS it lasted on average 52.7 ± 17.6 min ($P < 0.0001$). There were 1 ASA 1, 25 ASA 2, and 15 ASA 3 patients in the endarterectomy group compared with 25 ASA 2, 45 ASA 3, and 2 ASA 4 patients in the endovascular group; the anesthesiologic and surgical characteristic of the studied cohort presented statistically significant differences of ASA classification and duration of carotid flow arrest, while the proportion of episodes of new neurological deficits during surgery measured as inability to perform squeeze test did not reach the level of significance (Table II). One stroke was reported during postoperative period in each group with documented ischemic lesions at brain imaging

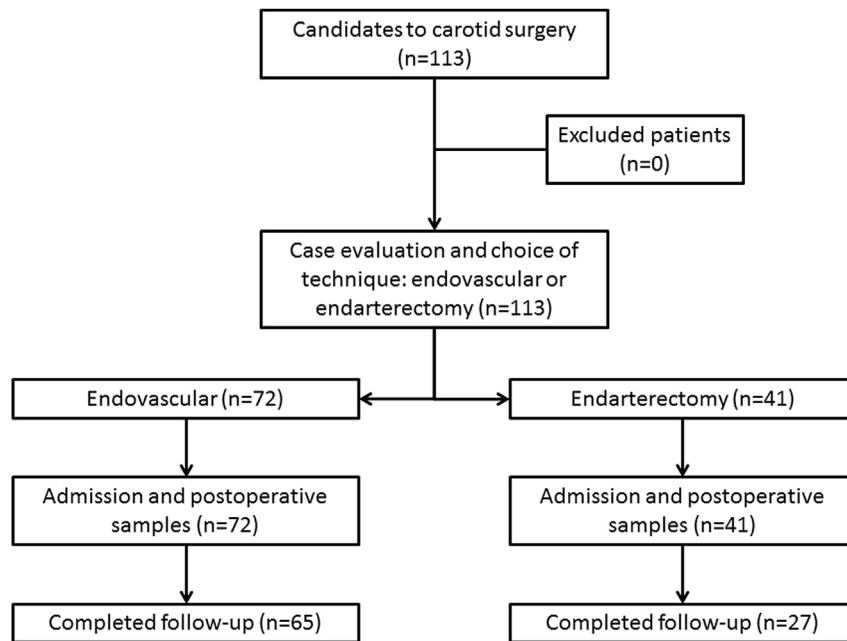


Fig. 1. Enrollment flowchart.

Table I. Patient demographics for endarterectomy and endovascular groups

Demographics	Endarterectomy (n = 41)	Endovascular (n = 72)	P value
Age (years)	71.0 ± 1.3	75.5 ± 0.9	0.0047
Sex (male)	70.7%	59.7%	0.242
Tobacco smoke	24.4%	18.1%	0.421
Dyslipidemia	56.1%	43.1%	0.182
Diabetes	17.1%	27.8%	0.199
Hypertension	70.7%	81.9%	0.167
AMI	14.6%	25.0%	0.195
TIA	19.5%	16.7%	0.703
Stroke	34.1%	20.8%	0.119
PAD	14.6%	36.1%	0.015

TIA, transient ischemic attack.

Age is expressed as mean ± standard deviation; for the categorical variables, percentages are given as a proportion of the patients who had the characteristics.

and permanent sensory and motor deficit at one hemisoma.

Table III summarizes the complications related to surgery identified during the follow-up; no statistically significant differences of prevalence were present between the 2 groups.

The baseline levels of the studied biomarkers did not show any statistically significant difference between groups with the exception of MMP-9, which showed higher concentrations in the endovascular group (median 731 vs. 401, $P = 0.0007$). Postoperative levels of MMP-9, S100 β , and D-dimer were

Table II. Surgical characteristics of the studied cohort

	Endarterectomy (n = 41)	Endovascular (n = 72)	P value
ASA	2 (2–3)	3 (2–3)	0.0038
Clamp (min)	41.5 (29.5–50)	7.5 (5–10)	<0.0001
Squeeze test failure (%)	21.9%	12.5%	0.158

ASA and clamp are expressed as median and interquartile range; for the categorical variables, percentages are given as a proportion of the patients who had the characteristics. There were 1 ASA 1, 25 ASA 2, and 15 ASA 3 patients in the endarterectomy group compared with 25 ASA 2, 45 ASA 3, and 2 ASA 4 patients in the endovascular group. Seven of the 9 patients who failed to perform the squeeze test in the endarterectomy group were used a shunt to partially restore carotid blood flow. The differences of the distributions of the continuous variables were assessed by the Wilcoxon's rank-sum test, while for the categorical variables χ^2 test was used. Clamp, duration of carotid flow arrest; squeeze test failure, percentage of patients who failed the squeeze test.

significantly higher in the endarterectomy group. D-dimer was the only marker to be higher after surgery in the endovascular group. This profile is compatible with a profile of increased inflammation and astrocyte damage in the endarterectomy group (Fig. 2).

A Wilcoxon rank-sum test was performed to assess the differences in concentration of the studied biomarkers in the individuals who failed the

Table III. Main complications reported during the follow-up period for each group (no statistically significant difference in the prevalence of complications was present between groups)

Groups	Follow-up		
	1 week (no. of cases)	1 month (no. of cases)	6 months (no. of cases)
Endovascular (<i>n</i> = 72)	Reduction of muscle power of the contralateral upper limb (1) Bleeding with hematoma of puncture site (1)	Death because of ischemic stroke (1)	Death because of sepsis (1)
Endarterectomy (<i>n</i> = 41)	Hypoglossal nerve involvement (2) Upper limb palsy with thrombosis of the operated vessel (1) ^a	Ischemic stroke (1) ^a	Death because of cerebral hemorrhage (1)

^aSame patient.

squeeze test within each group: there was a statistically significant difference between D-dimer postoperative levels in the endarterectomy group (median in failure subgroup 1886 vs. 818 ng/mL, $P = 0.0304$). Similarly, a statistically significant difference was shown between postoperative S100 β levels in those subjects where shunt was used during endarterectomy (0.083 μ g/mL in the shunt subgroup vs. 0.055 μ g/mL, $P = 0.0066$).

The Spearman's rank correlation test was used to assess the relationship between the level of the studied biomarkers at 24 hr and the duration of carotid flow arrest: no statistically significant correlations were observed between the concentrations of the 3 biomarkers included in this panel at 24 hr and the duration of carotid flow arrest.

DISCUSSION

Carotid surgery is one of the main vascular interventions. CEA is considered the gold standard technique for symptomatic stenosis, while CAS is indicated only for selected cases as its generalized application is controversial.^{3,4} In fact, randomized trials have demonstrated an excess in complications for the endovascular treatment when compared with open surgery.^{10,11} Paraskevas et al.²² in the critics to the CREST study have shown a substantial superiority of CEA versus CAS, but in their conclusions they emphasized that CREST used outdated technology and indications. Under this perspective, this study investigates the effects of the implementation of new technical solutions to CAS from a biomarker's point of view.

However, the CAS is characterized by shorter duration of the procedure and the potential for reduced invasivity. Factors that may influence the outcome of CAS are the experience of the operator and the anatomical and clinical characteristics of

the patient, which make them suitable for an endovascular approach: randomization may be especially challenging because standard evaluation methods (angiography and echocolor Doppler) could fail to identify conditions that contraindicate CEA or CAS. Epiaortic vessels angio-CT with analysis of the Willis circle, carotid plaque composition are often necessary to identify patient suitable for CAS. The adoption of specific devices (guide catheters and cerebral protection devices) makes CAS a feasible approach also in patients over 65 years of age, reducing some of the most common complications^{23–25} CAS still remains a technique for selected cases²⁶ but a careful preoperative assessment can extend its application to larger portion of patients, who may benefit from the reduced invasivity and duration of an endovascular approach when compared with open surgery.

The rate of reported complications seems comparable between groups, especially when considering the endovascular procedures.¹¹

Mantese et al.⁶ showed that age was the only parameter affecting treatment efficacy in CAS versus CEA for carotid surgery but the adoption of additional cerebral protection devices and specific guidewires may improve the efficacy of CAS in patients over 70 as suggested current data. In fact contrary to what are the actual indications to CAS, the present endovascular group was characterized by older age and a higher prevalence of PAD, as a less invasive approach was preferred in higher comorbidity patients with suitable anatomy, as reflected also by the ASA physical status classification assessment. The shorter duration of the procedure, the feasibility with local anesthesia, so without the need for mechanical ventilation, were considered beneficial factors in the perioperative management of these individuals, as an attempt to reduce the impact on the homeostasis of the elderly vascular patient. In fact, in these subjects complications can

PANEL OF BIOMARKERS

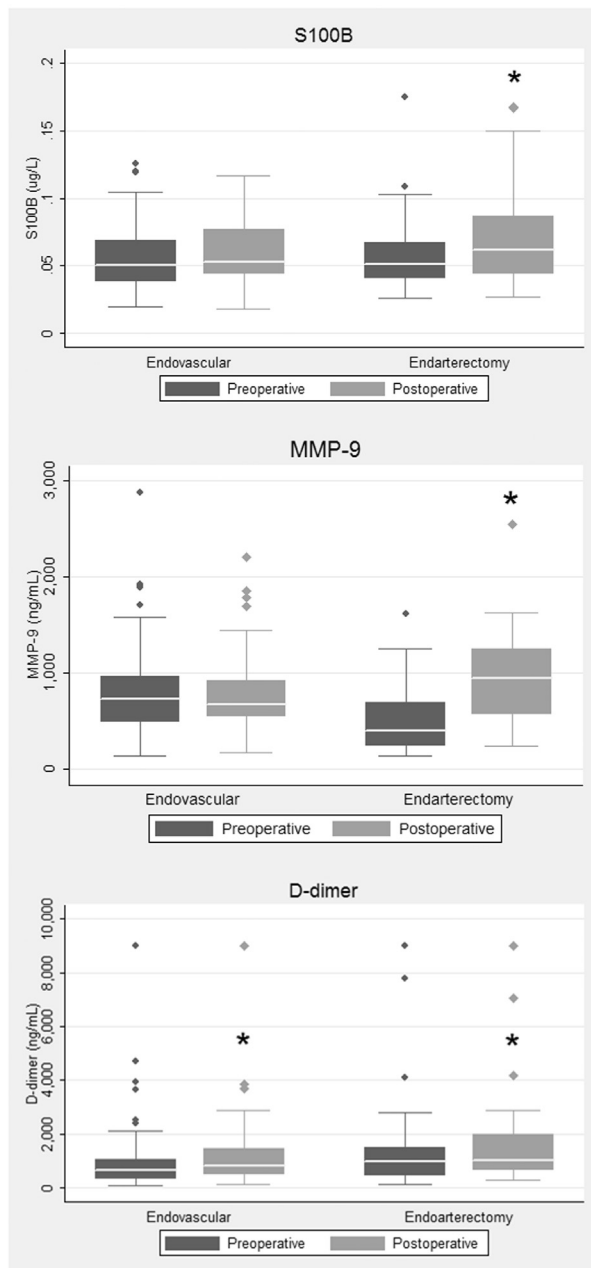


Fig. 2. Panel of biomarkers: data regarding S100 β protein, matrix metalloproteinase-9, and D-dimer peripheral blood levels, at baseline (preoperative) and 24 hr after surgery (postoperative), are reported as median with interquartile range for the endovascular and endarterectomy groups.

be related to factors not directly linked to the surgical procedure.

The studied biomarkers showed a significant increase from baseline in the open surgery group, even if this was, apparently, not related to the

duration of carotid flow arrest. D-dimer, which reflects the activation of the coagulation cascade, raised in both groups likely as a consequence of carotid atherosclerosis and activation of the fibrinolytic cascade²⁷ during and after surgery.

The correlation between the serum/plasma concentrations of a panel of specific biomarkers with neural damage has already been demonstrated. Here, we propose that their application to vascular surgery, especially to carotid interventions, can contribute to detect subclinical lesions that may not have direct consequences in the short term but can manifest as neurological status deterioration on a longer term. Postoperative cognitive impairment is associated to carotid surgery because of possible emboli that may detach from the carotid plaque during the procedure and the underlying clinical condition of the patient that may predispose him to the development of cerebrovascular pathologies.

S100 β peripheral levels, although characterized by a half-life of 25 min, have shown a good correlation with cerebral lesions 24 hr after cardiac surgery²⁸; elevated levels of this protein have been described after CEA probably as consequence of transitory episodes of cerebral hypoperfusion²⁹ and carotid clamping.³⁰ Contrary to what reported by Brightwell et al.,²⁹ our data show that the treatment modality affected S100 β peripheral levels 24 hr after the operation only in the CEA group. These findings were not related to the length of the carotid flow arrest, so they may be dependent on a more effective proximal cerebral protection strategy, which, however, calls for further assessment.

MMP-9, a gelatinase, peaks during CEA in correlation to vessel occlusion³¹: it is a marker of inflammation and damage of the blood–brain barrier therefore its postoperative increase could be related to microembolization and/or transient brain tissue damage. Other conditions may influence the concentration of MMP-9, such as chronic inflammatory diseases, tumors, and venous diseases, but the study compared a preoperative concentration with a postoperative level and it is unlikely that these confounding conditions are manifested in the 48-hr interval between samples collection.

MMP-9 adds value to the panel of markers as it explores the inflammation and alteration of the blood–brain barrier that is likely affected during surgery.

Interestingly, in this study, the levels of MMP-9 were significantly higher in the CAS group. This suggests a higher “baseline” inflammatory state or silent areas of damage associated with subclinical

blood–brain barrier dysfunction in this group of patients. Nevertheless, the incidence of neurological deficits did not differ in the 2 groups both during surgery and the 6-month follow-up.

The present data show that the endovascular approach determined a minor release of neural damage biomarkers than traditional open surgery for factors independent from carotid flow arrest duration but probably related to intrinsic characteristics of the procedure somehow entailing an improved cerebral protection, as shown by Montorsi et al.²¹ with a reduced rate of microembolization associated with the use of a proximal protection device. However, the statistically shorter duration of carotid flow arrest experienced during the endovascular procedures may have presumably led to a reduced neural damage, as highlighted by the biomarkers' trend.

The detection of intraprocedural microembolic events with transcranial Doppler could be correlated to the peripheral concentration of the studied biomarkers to provide further validation of this approach.

Limitations

The relatively small group of patients studied, enrolled in a single center, may limit the extent of the conclusions. Randomization was not implemented because of the substantially different surgical characteristics peculiar to patients suitable for endovascular surgery, which would bias the outcome of the procedures. Even if randomization would have been the best option in statistical terms, the highly individualized diagnostic work-up tailored on the clinical profile of the patients made it incompatible with an investigation on biomarkers.

The panel of markers could have comprised other neuron-specific markers and integrated their levels with imaging data to improve the diagnostic accuracy.

CONCLUSIONS

Peripheral neural damage biomarkers, an auxiliary diagnostic tool in the detection of subclinical lesions, demonstrated a substantial difference between open and endovascular carotid surgery, which, if performed in selected patients, may become a less invasive alternative to CEA. Data from this study do not support previous literature results obtained in randomized trials showing an excess in complications for the endovascular treatment when compared with open surgery. These findings would call for

further investigation to better assess the relationship between open and endovascular surgery and clinical neural damage, both in the acute phase and during follow-up.

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