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Subtle Cerebral Damage after Shunting vs Non Shunting during Carotid Endarterectomy

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Objective. *To compare the extent of subtle cerebral damage (SCD) in patients undergoing carotid endarterectomy with or without shunt placement.*
Design. *Prospective, randomised study.*
Patients and methods. *We assessed a consecutive series of 96 patients undergoing endarterectomy for severe unilateral left carotid stenosis who had been randomly assigned to receive a shunt (48) or not (48). Eligibility criteria included age up to 80 years and Mini-Mental State Examination score >24 points. Patients underwent neuropsychological testing before surgery. Serum concentrations of S100 protein, neuron-specific enolase (NSE) and interleukin-6 (IL-6) were measured intraoperatively before and after carotid clamping. Finally, each patient underwent neuropsychological testing 3 weeks after surgery.*
Results. *Patients with and without shunt had similar serum concentrations of S100 protein, NSE and IL-6 as well as similar neuropsychological test scores, all* $p > 0.05$.
Conclusions. *There was no difference in subtle cerebral damage between patients randomized to receive a shunt or not.*
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Keywords: Carotid stenosis; Carotid endarterectomy; Subtle cerebral damage; Neuropsychological test.

Introduction

Carotid endarterectomy (CEA) has an important role in the management of extracranial carotid artery stenosis. In particular, CEA is the best option for treating severe stenosis (equal to or greater than 70%) in both asymptomatic[1,2] and symptomatic patients.[3,4]

Some issues concerning CEA have been under debate for several years, including the important question of cerebral tolerance to temporary carotid occlusion (carotid clamping) during CEA. Several methods (such as stump pressure, electroencephalography, somatosensory evoked potentials, neurologic monitoring in awake patients, etc.) have been proposed for assessing the effects of carotid clamping on haemodynamics or brain function.

Shunting is generally considered the best way of avoiding carotid clamping-associated cerebral ischaemia during CEA. Nevertheless, there is no evidence that shunting ensures better results versus non-shunting.[5] Currently, selective shunting during CEA is quite widespread, while routine shunting or non-shunting are carried out less frequently.

There is considerable controversy regarding whether routine or selective shunting yields better results in CEA. We know that cerebral hypoperfusion during carotid clamping causes an inflammatory response. The most severe complication of cerebral hypoperfusion is stroke of haemodynamic origin, with an incidence ranging from 0.2% to 7.6%.[6,7]

Even in the absence of an obvious perioperative stroke, minimal subtle cerebral damage (SCD) due to hypoperfusion may occur in some patients. This is a well known possible complication of cardiac surgery[8] which can lead to impairment that is detectable by detailed neuropsychological testing. We must stress that subtle cerebral damage (SCD) leads to cognitive impairment and is an underestimated complication of CEA.

The aim of our prospective, randomised study was to assess the relationship between cerebral hypoperfusion during carotid clamping and SCD. A group without cerebral protection during carotid clamping

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(non-shunted patients) was compared to a group with cerebral protection during CEA (shunted patients).

In order to compare the incidence of SCD in non-shunted and shunted CEA patients, we performed laboratory tests designed to detect cerebral ischaemia, as well as neuropsychological tests.

Patients and Methods

Between February 2006 and September 2006, 149 CEAs were carried out. We enrolled 96 consecutive, eligible patients from among this group into our study (Table 1). The patients presented the following characteristics: unilateral severe (equal to or greater than 70%) carotid stenosis, left side involvement in right-handed patients, age up to 80 years, preoperative Mini-Mental State Examination (MMSE)[9] score >24 points (Table 2). Only left carotid stenoses were taken into consideration since the left cerebral hemisphere is dominant in more than 98% of right-handed persons.[10] The degree of stenosis was assessed by duplex scanning according to haemodynamic criteria.[11] Based on the presence or absence of a history of ipsilateral amaurosis fugax, focal transient deficit or minor stroke of the ipsilateral cerebral hemisphere, carotid stenosis was considered either asymptomatic or symptomatic, respectively. CEA was carried out five days to six weeks after the ischaemic episode (TIA in 21 cases, amaurosis fugax in 6, and minor stroke in 6) in symptomatic patients.

Exclusion criteria were contralateral severe carotid stenosis or carotid occlusion, right side involvement, age greater than 80 years, dementia, previous disabling stroke, brain tumours, neuroleptic therapy, and MMSE score <24 points.

Each patient was evaluated by clinical examination (including neurological examination carried out by a neurologist), duplex scanning, cerebral computed tomography (CT), and by neuropsychological tests (listed in Table 3), performed by a psychologist prior to surgery.

Table 1. Characteristics of study patients

	Non-shunted group	Shunted group
Patients	48	48
Males/females	31/17	33/15
Age range (mean)	55–80 (71.4)	59–80 (71.5)
Left severe carotid stenosis asymptomatic/symptomatic	31/17	32/16
Smoking	39/48	40/48
Heart disease	21/48	18/48
Hypertension	40/48	41/48
Diabetes	9/48	8/48
Hypercholesterolaemia	23/48	27/48
Mini-Mental State Examination score	27.2 ± 1.3	27.4 ± 1.1

Table 2. Mini-Mental State Examination

	Score
Orientation	
What year, season, date, day, month is it? (Score 1 point for each correct answer)	5
Where are we: country, city, part of city, number of flat/house, name of street? (Score 1 point for each correct answer)	5
Registration	
Name three objects: say each one in one second, then ask the patient to name all three after you have said them. (Score 1 point for each correct answer)	3
Attention and calculation	
Serial 7s. Stop after five answers. (Score 1 point for each correct answer)	5
Recall	
Ask for the three objects repeated above. (Score 1 point for each correct answer)	3
Language	
Name a pencil and watch.	2
Repeat the following: 'No ifs, ands, or buts'.	1
Follow a three-stage command: 'Take a paper in your right hand, fold it in half and put it on the floor.	3
Read and obey the following: Close your eyes.	1
Write a sentence.	1
Copy a design.	1

Multilayer, high-resolution cerebral CT was used with three-dimensional reconstruction. Preoperative cerebral CT was positive for ischaemic lesions in 18/48 (37.5%) cases of the non-shunted group and in 14/48 (29.2%) of the shunted group. Eight patients in the non-shunted group showed lesions in the ipsilateral cerebral hemisphere, while an additional 10 patients had bilateral hemispheric lesions. Eight patients in the shunted group had ipsilateral cerebral hemisphere lesions, 4 presented with contralateral lesions and 2 with bilateral lesions. Among the patients with ischaemic lesions (32 cases), 12 were neurologically asymptomatic (7 in the non-shunted group and 5 in the shunted group), while 20 were symptomatic (TIA in 13, amaurosis fugax in 3, and minor stroke in 4).

All patients were randomly assigned to either the non-shunted or to the shunted group. Randomisation was done by a random number generator using computational method that was managed by a statistician. After preoperative evaluation including grade of carotid stenosis, side of involvement and MMSE, the patients fulfilling the inclusion criteria were enrolled in the study, and underwent cerebral CT and neuropsychological testing. Randomisation of each patient was made immediately before carotid endarterectomy.

All patients were operated on under general anaesthesia using inhalation anaesthetics (sevoflurane), intravenous sedative-hypnotic agents (propofol),

Table 3. Preoperative and postoperative (three weeks after surgery) neuropsychological tests

Neuropsychological tests	Technique
Stroop Colored Word Test	The patient is asked to say the ink colour of each item out of a given list
Reaction Times in Simplex and Complex Tasks	The patient has to recognise a visual input on a screen
Go No Go Test	The patient has to press a button when he/she sees the target item on a screen
Splitted Attention Test	The patient must recognise a complex visual configuration on a screen in random times
Posner Test	The patient is asked to reply to a repeated series of individual inputs submitted in the right or left visual field
Trail Making A and B	The patient is asked to carry out a duty concerning progressive numbering (A) and to connect numerical and alphabetical elements alternatively (B)
Test of Verbal Fluency	The patient is asked to say the greatest number of words he/she can think of that begin with a given letter
Working Memory Test	The patient is asked to recognise numbers given one by one, detecting when the number currently shown is the same as the last but one
Verbal Memory Span	The operator says two disyllabic words, then three words, and so on increasing. The patient is asked to repeat the words in the same order.

analgesics (fentanyl), and muscle relaxants (atracurium). Vasopressor (ephedrine) and/or vasodilator (nitroglycerine) was administered on the basis of blood pressure changes.

Surgery was carried out via the presternocleidomastoid route. The carotid arteries were exposed and heparin sodium was administered intravenously (5000 IU) prior to carotid clamping. Stump pressure was evaluated in all cases. CEA was performed using the eversion technique. Pruitt–Inahara shunt was used in the shunted group. Endarterectomy was completed in the internal, external, and common carotid arteries using microsurgical instruments.

Serum concentrations of S100 protein, neuron specific enolase (NSE) and interleukin-6 (IL-6) were measured before and after carotid clamping by taking blood samples from the left internal jugular vein. All patients underwent cerebral CT three days after surgery to rule out any significant damage. They also underwent repeat neuropsychological testing by the psychologists three weeks after surgery.

Our Institute's ethics committee approved the study protocol. All patients enrolled in the study were adequately informed and consented to participate in the study.

The two groups were compared with regards to gender, age, clinical state (asymptomatic or symptomatic) of carotid stenosis, and risk factors by using unpaired t-test and chi-squared test for comparison of means and percentages, respectively (level of significance 5%). Moreover, we have analysed differences between the two groups with regards to pre-clamping and post-clamping serum concentrations of S100 protein, NSE, and IL-6, as well as to preoperative and postoperative neuropsychological tests by the Mann–Whitney U test for non-parametric data (level of significance set at 5%).

Results

There were no differences between the two groups regarding demographic characteristics and risk factors ($P > 0.05$).

All patients underwent the allocated treatment and no patients in the no shunt group required shunting. Stump pressure in all 96 cases resulted equal to or greater than the threshold of 50 mm Hg, which did not require shunting according to our policy (stump pressure below 50 mm Hg).

Carotid clamping time was 23–145 min (mean 61) in the non-shunted group, while in the shunted group it was 4–15 min (mean 7) before shunt insertion, and 3–10 min (mean 7) from shunt removal to carotid declamping.

No perioperative major strokes or deaths occurred in either group. Two transient ischaemic attacks (upper extremity monoparesis in one case and dysphasia in the other case) were observed.

No significant differences ($P > 0.05$) were found between the two groups preoperatively in cerebral CT findings. Postoperative cerebral CT did not show any new lesions in either group. There were no significant differences between the non-shunted group and the shunted one with regards to both pre-carotid clamping and post-carotid clamping serum concentrations of S100 protein, NSE, and IL-6 (Table 4). Finally, we did not observe any statistical differences between the two groups before surgery and after CEA with regards to neuropsychological tests (Table 5).

Discussion

Perioperative stroke and death rates as well as long term, stroke-free periods are the usual parameters

Table 4. Serum concentrations (expressed as means ± standard deviation) of S100 protein, neuron specific enolase, and interleukin-6. Comparisons were performed between the non-shunted group and the shunted group preoperatively and postoperatively by the Mann–Whitney U test for nonparametric data (level of significance 5%)

Laboratory tests	Non-shunted group	Shunted group	*P* value
S100 protein	preop. 3.22 ± 2.98	preop. 3.29 ± 2.16	0.44
	postop. 3.36 ± 1.22	postop. 3.35 ± 2.01	0.79
Neuron specific enolase	preop. 5.95 ± 4.50	preop. 6.22 ± 3.50	0.40
	postop. 6.93 ± 4.00	postop. 6.72 ± 4.50	0.75
Interleukin-6	preop. 27.37 ± 8.40	preop. 16.52 ± 8.62	0.45
	postop. 33.54 ± 9.48	postop. 20.68 ± 6.50	0.40

for measuring the safety and efficacy of CEA. Although numerous studies have examined the effects of carotid clamping and methods of cerebral protection, little attention has been paid to subtle cerebral damage which may complicate CEA and lead to impairment of post CEA cognitive function. Inconsistent and controversial results have been reported about effects of CEA on cognitive function. Bornstein *et al.*,[12] Antonelli Incalzi *et al.*,[13] and Fearn *et al.*[14] reported some improvement in neuropsychological functions after CEA. On the contrary, studies by Iddon *et al.*,[15] and Pearson *et al.*[16] showed no improvement following CEA. Monomen *et al.*,[17] Heyer *et al.*,[18] and Sinforiani *et al.*[19] demonstrated improvement in some neuropsychometric tests and impairment (or no change) in other neuropsychological parameters. These varying results are likely due to methodological problems with the study of cognitive function before and after CEA, as well as to wide disagreement in the interpretation of results. Given the conflicting results and the methodological issues, it is not possible to draw a clear conclusion regarding the impact of CEA upon cognitive function. Future research focusing on methodological factors is needed in order to adequately resolve this debate.

Our study was developed by applying neuropsychological testing in order to determine whether cerebral hypoperfusion during CEA causes SCD. A wide series of neuropsychological tests were chosen to explore several cognitive functions, such as visual, numerical, and verbal activities. This choice allowed us to exclude erroneous observations based on one test alone. Our results strongly support the theory that cerebral hypoperfusion does not generate SCD in the short-term after CEA.

Further information on ischaemic changes caused by CEA could be provided by diffusion-weighted magnetic resonance, which is well-known for its sensitivity

Table 5. Neuropsychological tests three weeks after surgery. The values are expressed as means ± standard deviation. Comparisons were performed between the non-shunted group and the shunted group preoperatively and postoperatively by the Mann–Whitney U test for nonparametric data (level of significance 5%)

Neuropsychological tests	Non-shunted group	Shunted group	*P* value
Stroop Colored	preop. 4.27 ± 2.15	preop. 5.17 ± 3.17	0.29
Word Test	postop. 4.22 ± 2.24	postop. 5.49 ± 3.01	0.78
Reaction Times in Simplex and	preop. 351.08 ± 108.55	preop. 377.59 ± 130.54	0.43
Complex Tasks	postop. 351.40 ± 102.35	postop. 344.05 ± 94.48	0.78
Go No Go Test	preop. 13.62 ± 2.26	preop. 13.00 ± 3.03	0.95
	postop. 13.38 ± 2.15	postop. 13.58 ± 1.67	0.97
Splitted Attention Test	preop. 2.04 ± 1.03	preop. 2.02 ± 1.14	0.95
	postop. 1.58 ± 1.08	postop. 1.53 ± 0.54	0.74
Posner Test			
Target on right	preop. 424.06 ± 74.56	preop. 457.41 ± 116.42	0.29
	postop. 455.78 ± 167.46	postop. 450.82 ± 93.97	0.89
Target on left	preop. 463.17 ± 94.60	preop. 488.85 ± 80.50	0.59
	postop. 587.28 ± 293.31	postop. 533.52 ± 162.12	0.27
Trail Making A and B Test			
Part A	preop. 1.27.82 ± 0.46.08	preop. 1.17.52 ± 0.28.70	0.33
	postop. 1.22.51 ± 0.34.52	postop. 1.09.52 ± 0.27.48	0.14
Part B	preop. 3.59.86 ± 2.22.92	preop. 3.58.92 ± 2.16.63	0.98
	postop. 4.09.43 ± 2.16.21	postop. 3.39.89 ± 2.15.26	0.43
Test of Verbal Fluency	preop. 11.20 ± 3.54	preop. 10.48 ± 3.79	0.48
	postop. 12.46 ± 3.65	postop. 11.38 ± 3.86	0.30
Working Memory Test	preop. 5.31 ± 1.51	preop. 4.73 ± 1.75	0.47
	postop. 5.58 ± 1.47	postop. 5.58 ± 1.41	0.12
Verbal Memory Span	preop. 3.65 ± 0.62	preop. 3.85 ± 0.46	0.21
	postop. 3.77 ± 0.51	postop. 3.96 ± 0.34	0.61

in detecting brain ischaemia.[20] In addition to neuropsychological tests, we also used laboratory tests in our study. These tests, i.e., S100 protein, NSE and IL-6 are considered markers of cerebral ischaemic damage.[21–27] Some doubts have been raised regarding the reliability of S100 protein and NSE as markers of cerebral damage.[21,22] In our study there were no differences between the shunted and non-shunted patients with respect to S100 protein, NSE, IL-6, or neuropsychological testing. These findings are inconsistent with those of Parsson *et al.*,[28] who observed inflammatory response to carotid clamping in non-shunted cases. These authors performed their study using different laboratory tests (such as interleukin-1beta, phospholipase A, thromboxane B, 6-keto-prostaglandin F1alpha and prostaglandin). However, as in our study, however, Parsson *et al.* did not find any cognitive impairment in non-shunted patients, despite the metabolic changes that were observed.

Our study failed to demonstrate an association between SCD and shunt use or non-use. One potential conclusion that may be drawn from our data is that SCD is related to microembolisation and not to subclinical cerebral ischaemia during carotid clamping. Our results may be linked to two essential factors: general anaesthesia and usefulness of shunt. In fact, general anaesthesia provides brain protection with respect to haemodynamics and metabolism.[29] On the basis of our results, routine shunting during CEA would not appear justifiable if there is no need for shunting based on the assessment of cerebral tolerance to carotid clamping. In addition, CEA without shunting prevents some possible complications (dissection, microembolism, and thrombosis).

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