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Cognitive improvement in patients with carotid stenosis is independent of treatment type

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Summary

Treatment of carotid artery stenosis decreases the long-term risk of stroke and may enhance cerebral blood flow. It is therefore expected to have the potential to prevent cognitive decline or even improve cognition over the long-term. However, intervention itself can cause peri-interventional cerebral infarcts, possibly resulting in a decline of cognitive performance, at least for a short time. We investigated the long-term effects of three treatment methods on cognition and the emotional state one year after intervention.

In this prospective observational cohort study, 58 patients with extracranial carotid artery stenosis (≥70%) underwent magnetic resonance imaging and assessment of cognition, mood and motor speed before carotid endarterectomy (n = 20), carotid stenting (n = 10) or best medical treatment (n = 28) (i.e., time-point 1 [TP1]), and at one-year follow-up (TP2). Gain scores, reflecting cognitive change after treatment, were built according to performance as (TP2 −TP1)/TP1.

Independent of the treatment type, significant improvement in frontal lobe functions, visual memory and motor speed was found. Performance level, motor speed and mood at TP1 were negatively correlated with gain scores, with greater improvement in patients with low performance before treatment.

Active therapy, whether conservative or interventional, produces significant improvement of frontal lobe functions and memory in patients with carotid artery disease, independent of treatment type. This effect was particularly pronounced in patients with low cognitive performance prior to treatment.

Key words: *carotid artery stenosis; cognitive function; emotional state; endarterectomy; stenting; best medical treatment*

Introduction

Cognitive performance is an important outcome measure of carotid artery treatment and affects patient well-being and quality of life. High-grade stenosis of the carotid artery is associated with cognitive impairment [1], even when there is no evidence of infarction on magnetic resonance imaging (MRI). Likely mechanisms for such cognitive effects are multiple and include embolisation and chronic or intermittent hypoperfusion distal to the stenosis. Interestingly, some patients display normal cognitive performance despite severe carotid artery disease [1]. At present, carotid artery disease is usually treated with carotid endarterectomy (CEA), carotid artery stenting (CAS) or best medical treatment (BMT).

Reports on the effect of carotid artery treatment on cognition are inconsistent. Some studies claim an increase of cognitive performance after CEA in certain cognitive domains [2, 3], others propose a cognitive decline [4, 5], and some describe no performance change after CEA [6]. Recent reviews [7–9] concluded that neither CEA nor CAS clearly affected cognition in general and that there were no differences in overall cognitive functioning after CEA or CAS. However, a definitive conclusion regarding the effect of CAS versus CEA on cognitive function is impossible owing to heterogeneity in definition, method, timing of assessment and type of cognitive tests.

Time at follow-up varied widely across studies, with follow-up ranging from 24 hours to 12 months [8]. More time between carotid stenosis treatment and follow-up as-

sessment is reported to be associated with greater cognitive improvement [10, 11]. Therefore, the time-window between treatment and follow-up might be a crucial factor for evaluating cognitive change after carotid stenosis treatment.

Regarding the emotional state of patients with carotid artery disease, several studies indicate an improvement after treatment of carotid stenosis: lower depression scores were observed after CAS [12] and better mental health scores were observed after CEA [13]. These improvements are likely due to the emotional relief of a reduced risk of stroke and psychological relief after uncomplicated treatment [6].

In this study, we compared the long-term effects of different invasive revascularisation methods (CEA, CAS) and BMT on cognition, and describe for the first time in the literature the long-term effects of three different treatment methods on the emotional state of patients with carotid artery disease. Findings of cognitive or emotional long-term improvements would support the efficacy of carotid artery disease treatment.

Methods

Cohort and study design

Between 2009 and 2012, specialised interdisciplinary clinical teams at two university hospitals recruited 95 in- or outpatients with significant carotid stenosis (≥70%) on any noninvasive examination (Doppler, computed tomography angiography or magnetic resonance [MR] angiography). Patients were considered symptomatic if a minor stroke [14], retinal ischaemia or transient ischaemic attack (TIA) with motor, sensory, speech or visual impairment had occurred within 3 months prior to inclusion. Asymptomatic patients were defined as having no previous minor stroke or TIA. Patients had to consent to the study and be able to undergo a standardised cognitive assessment and an MRI examination before possible treatment of carotid artery disease (time point 1; TP1, as described elsewhere [1]) and at one-year follow-up (time point 2; TP2). A one-year follow-up period was chosen to gain insight into the long-term outcome of patients after noninvasive treatment of carotid artery disease.

Exclusion criteria were: major stroke, carotid stenosis <70%, significant handicap at the time of inclusion as measured by a modified Rankin Scale score >2, progressive cerebral pathology (such as tumour, multiple sclerosis, Alzheimer's disease), and standard exclusion criteria for MRI investigations. Local ethics committees of the responsible centres approved the study protocol. Written informed consent was obtained from all patients prior to study inclusion.

Clinical assessment

The degree of carotid artery stenosis was determined based on Duplex ultrasound. Peak systolic velocities of >215 cm/sec were graded as stenosis of ≥70%, which is equivalent to a stenosis of ≥70% according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) [15, 16]. If Duplex data were unavailable, data from digital subtraction angiography, computed tomography angiography or MR angiography were used to grade stenoses, also according to NASCET criteria [15]. High resolution 1.5 Tesla MRIs were analysed to score the severity of white matter hyperintensities (Fazekas rating scale, Age-Related White Matter Changes (ARWMC) scale [17–19]) and to document structural brain lesions caused by trauma, haemorrhage, old infarction, infection or tumour, in particular in symptomatic carotid artery disease (table 1). On T1 weighted images the relative white and grey matter volumes were calculated (Statistical Parametric Mapping 8, SPM8; www.fil.ion.ucl.ac.uk/spm/ for MATLAB R2009a, MathWorks, Natick, MA, USA). Collateralisation was assessed by categorising the completeness of the circle of Willis as determined on time-of-flight MR angiography images. The completeness of the circle of Willis was categorised into three groups according to Ryan et al. 2013 [20]: classical complete, hypoplastic and incomplete circle of Willis. For details regarding the association between the collateralisation and cognitive assessment at TP1 see [1]. The National Institute of Health Stroke Scale (NIHSS) was assessed to evaluate the neurological status of the patients. Vascular risk factors were assessed by physicians during an interview (see table 1).

Cognitive assessment

The cognitive assessment comprised 13 cognitive domains (printed below in italics). In the domain of executive functions, *interference control* (Stroop Interference [21]), *processing speed* (Symbols [22]), and *verbal fluency* (Animal Naming; [23]) were assessed. *Word production* was assessed with the Boston Naming Test [23]. Furthermore, different memory domains such as *verbal learning, recall and recognition* (Word Rey Learning Tests; [24]), *short term memory* (Digit Span Test; [22]) and *visual learning, recall and recognition* (for patients >70 years Signs, [25]; for patients <70 years Rey Figure [26]) were assessed. *Motor speed* (Purdue Pegboard; [27]) and *emotional state* (Hospital Anxiety and Depression Scale [28]) were assessed (high scores represent high anxiety and/or depression). In all tasks higher scores reflect better performance, except for interference control, where lower scores indicate better performance. For a detailed description of cognitive performance before treatment see [1].

Therapy

Decisions about whether and which method of treatment was applied (CEA, CAS, BMT) were taken independently of the study and were up to the treating physicians and patients. In both centres, published European guidelines were followed [29]. There was a lower threshold to intervene (CEA or CAS) in patients with recent symptoms related to the stenosis, male patients, and high grade stenosis. In both centres, CEA is generally preferred in symptomatic and elderly patients. BMT included an antiplatelet agent, statin treatment to attain a low density lipoprotein cholesterol level ≤2.6 mmol/l, antihypertensive treatment to attain a blood pressure <140/90 mm Hg (diabetics: <130/85), strict control of hyperglycaemia if diabetic, counselling for smoking cessation, and basic information about weight control, regular physical exercise, and balanced nutrition.

Statistical analysis

*S*tatistical analyses were conducted using IBM SPSS Statistics 20.0. For all cognitive, motor speed and emotional state tests, raw scores were used for the analyses. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. The majority of the variables (except interference control and verbal learning, recognition and recall) were not normally distributed. Consequently, and also because of the different group sizes, non-parametric statistics were used to evaluate all variables. Two-sided probabilities are reported for all statistical tests. The Bonferroni method was used to counteract type I error caused by multiple comparisons [30]. Mann-Whitney-U tests were analysed to identify group differences between symptomatic and asymptomatic patients according to the MRI. To detect group differences among the three treatment groups (CEA, CAS, BMT) with regard to patient characteristics, the Kruskal-Wallis test was applied. Differences between cognitive performance at TP1 and TP2 were calculated using the Wilcoxon signed-rank test. Changes in cognitive performance between TP1 and TP2 are presented as relative gain scores, and approximate effect sizes are reported as *r*. The relative gain score is defined as ((TP2-TP1)/TP1). Gain score differences were analysed with Kruskal-Wallis tests (treatment groups, education level, side of stenosis) or Mann-Whitney-U tests (sex, condition). To analyse the relationship between age, performance level at TP1 and gain scores, Spearman correlations were performed. Sample size varied across different cognitive tasks due the fact that some tasks were only performed in patients ≥70 years (visual memory: Signs Learning Test) or in patients <70 years (visual memory: Rey figure).

Results

Of 95 patients who were initially recruited into the study at the two hospitals, 37 were excluded because of stenosis grade <70% (n = 13), intracranial instead of extracranial stenosis (n = 5), infarction larger than a third of the middle cerebral artery territory (n = 3), severe stroke (n = 2), or missing cognitive data (n = 6). One year after the first assessment, two patients had died and six patients did not want to continue in the study. Therefore, 58 patients were retained for further analyses (43 male, 15 female; mean age 69.4, range 51.4–85.3 years). There was no effect of age (over all raw scores Spearman correlations p >0.05), sex (Kruskal-Wallis tests p >0.05) or education (Mann Whitney-U tests p >0.05) on gain scores. The number of symptomatic or asymptomatic patients, sex, age, vascular risk factors, relative grey and white matter volume, hyperintensity, NIHSS scores and cognitive performance at TP1 showed no significant differences between treatment groups (table 2). White matter hyperintensities, and grey and white matter volumes, did not differ between symptomatic and asymptomatic patients (table 1).

For all groups combined, mean time between cognitive assessment and follow-up examination was 389 days (standard deviation [SD] 38, range 306–519 days). At time of treatment, 36 patients were asymptomatic. Among the 22 patients with symptomatic carotid artery stenosis, 44.5% had a TIA, 22.2% suffered from a minor stroke and 33.3% had retinal ischaemia. In symptomatic patients, the time interval to stroke or TIA had no influence on the gain scores in all cognitive tasks.

In the total group of patients, the mean score of all 13 cognitive tasks increased between TP1 and TP2. Significant improvement of cognitive performance occurred in 8 out of 13 cognitive tasks (61.5%) and in motor speed (dominant hand: $Z = –2.16$, p = 0.031, table 3). Emotional state did not improve significantly between TP1 and TP2 (anxiety: $Z = –1.15$, p = 0.249; depression $Z = –0.06$, p = 0.950).

Cognitive assessment at TP1 was performed in 20 patients before CEA (34.5%), in 10 patients before CAS (17.2%) and in 28 patients before BMT (48.3%). Patients of the CAS group improved in all cognitive tasks after one year; this was statistically significant in 4 of 13 tasks (p <0.05). Patients with CEA also improved in all cognitive tasks; this was statistically significant in 2 of 13 tasks (p <0.05). Patients with BMT improved in 11 of 13 cognitive tasks; this was statistically significant in 3 of 13 tasks (p <0.05). However, in the BMT group, performance showed a nonsignificant trend towards a decline in two cognitive tasks. Gain scores did not differ significantly among the three treatment groups in any of the cognitive tasks (see table 4).

Women had significantly higher gain scores in visual learning than men ($U = 38$, $Z = –2.02$, p = 0.043). Age correlated significantly with the gain score of word production ($r = –0.27$, p = 0.043), verbal recognition ($r = –0.31$, p = 0.019), verbal recall ($r = –0.32$, p = 0.014), visual learning ($r = –0.39$, p = 0.047) and short term memory ($r = –.26$, p = 0.049), with younger patients benefitting more from treatment. Presence of collaterals did not influence the gain scores of all tests.

Performance level at TP1, mood at TP1 and motor speed at TP1 were significantly correlated with gain scores in a negative way, such that greater improvement was observed in patients with low performance at TP1 (interference control: $r = –0.30$, p = 0.025; processing speed: $r = –0.47$, p <0.001; verbal fluency: $r = –0.38$, p = 0.003; short term memory: $r = –.37$, p = 0.004; verbal memory: $r = –.45$, p <0.001, visual learning: $r = –0.68$, p <0.001; visual recognition: $r = –.97$, p <0.001; visual Rey immediate recall: $r = –0.60$, p =

Table 1: Asymptomatic versus symptomatic patients.

	Asymptomatic n = 36	**Symptomatic n = 22**	**Group difference *Z* (p-value)**
ARWMC	4.37 (4.34)	4.95 (3.03)	–1.01 (0.311)
Fazekas scale	0.80 (0.79)	1.14 (0.73)	–1.72 (0.085)
Relative grey matter volume	1.01 (0.14)	0.99 (0.14)	–0.34 (0.733)
Relative white matter volume	1.00 (0.16)	0.99 (0.13)	–0.07 (0.946)

ARWMC = age-related white matter changes
Data are mean (standard deviation)

0.001; visual Rey late recall: $r = –0.38$, p = 0.042; anxiety: $r = –.40$, p = 0.003; depression: $r = –0.45$, p = 0.001, motor speed nondominant hand: $r = –.41$, p = 0.002). Hence, patients with low cognitive performance, low anxiety and depression or slow motor speed at TP1 benefitted most from endarterectomy.

The side of stenosis and the presenting symptoms (asymptomatic versus symptomatic) did not relate to performance at TP1, TP2 or gain scores. Time between treatment and follow-up was not associated with gain scores on any cognitive task. However, education level correlated with interference control, verbal fluency and word production at TP1 and TP2 (all: $r > 0.34$, p <0.05).

Discussion

The present study showed that, independent of the treatment type, significant improvement of executive functions, visual memory and motor speed can occur following treatment of carotid artery disease. Following BMT, improvement occurred in fewer cognitive tasks than after CEA or CAS. However there was no significant effect of treatment group with regard to cognitive performance level at 1-year

Table 2: Patients' characteristics.

	BMT n = 28	CAS n = 10	CEA n = 20	Total n = 58	Group differences *H*(2)/(p-value)
Demographics					
Age, mean (SD)	71.3 (8.1)	65.4 (9.3)	68.7 (7.9)	69.4 (8.4)	3.4 (0.18)
Male, n (%)	21 (75.0)	9 (90.0)	13 (65.0)	43 (74.1)	2.2 (0.34)
Asymptomatic, n (%)	20 (71.4)	4 (40.0)	12 (57.1)	36 (62.1)	3.1 (0.21)
Stenosis side, n (%)					
Right	11 (39.3)	6 (60.0)	9 (45.0)	26 (44.8)	1.9 (0.39)
Left	9 (32.1)	3 (30.0)	8 (40.0)	20 (34.5)	
Both	8 (28.6)	1 (10.0)	3 (10.0)	12 (20.7)	
Vascular risk factors, n (%)					
Hypertension	22 (83.3)	5 (50.0)	15 (75.0)	42 (72.4)	3.1 (0.22)
Diabetes	7 (25.0)	2 (20.0)	7 (35.0)	16 (27.6)	0.9 (0.63)
Hypercholesterolaemia	23 (82.1)	5 (50.0)	15 (75.0)	43 (74.1)	3.9 (0.14)
Coronary artery disease	10 (35.7)	6 (60.0)	6 (30.0)	23 (37.9)	2.6 (0.27)
Thrombophilia	0	0	1 (5.0)	1 (1.7)	1.9 (0.39)
Atrial fibrillation	2 (7.1)	0	2 (10.0)	4 (6.9)	1.0 (0.60)
Current smoking	5 (17.9)	2 (20.0)	5 (25.0)	12 (20.7)	0.4 (0.84)
Number of risk factors	2 (0–5)	2 (1–4)	2 (0-5)	2 (0-5)	1.7 (0.44)
Lesion analysis by structural MRI					
NIHSS score	0 (0–4)	0 (0-0)	0 (0-0)	0 (0–4)	3.8 (0.15)
Grey matter volume	1.02 (0.15)	1.04 (0.07)	0.96 (0.14)	1.00 (.14)	3.9 (0.14)
White matter volume	1.01 (0.17)	1.02 (0.14)	0.97 (.12)	1.00 (1.4)	0.7 (0.70)
Faszekas scale	1 (0–3)	1 (0–3)	1 (0–2)	1 (0–3)	1.4 (0.50)
ARWMC	5.51 (4.34)	4.70 (3.55)	3.37 (3.45)	4.59 (3.88)	3.9 (0.19)

ARWMC = age-related white matter changes; BMT = best medical treatment; CAS = carotid artery stenting; CEA = carotid endarterectomy; MRI = magnetic resonance imaging; NIHSS = National Institute of Health Stroke Scale
Data are mean (standard deviation), n (%) or median (range)

Table 3: Cognitive performance before (TP1) and after treatment (TP2; 1-year follow-up).

	TP1	TP2	*Z*	*r*
Interference control‡	76.5	69.0	–2.93**†	0.39
Processing speed	19.0	21.0	–1.82	0.24
Verbal fluency	18.0	21.0	–2.69**	0.35
Word production	23.0	26.0	–2.27*	0.29
Verbal learning	37.0	36.5	–0.46	0.06
Verbal recognition	11.5	12.0	–2.10*	0.27
Verbal recall	10.0	10.0	–1.20	0.15
Short term memory	5.5	6.0	–4.20***†	0.55
Visual learning	17.5	17.0	–0.29	0.05
Visual recognition	10.0	10.0	–2.27*	0.43
Visual recall	7.0	7.5	–0.34	0.07
Visual Rey immediate recall	20.0	24.8	–2.51*	0.46
Visual Rey late recall	20.0	24.8	–3.07**†	0.57

TP1 = cognitive assessment before treatment, TP2 = cognitive assessment at 1-year follow-up
Data are median raw scores
‡ In all tasks higher scores indicate higher performance, except in interference control where higher scores mean slower performance
* p <0.05, ** p <0.01, *** p <0.001
† p remains significant after Bonferroni correction

follow-up. These results suggest that the effects of treatment type on cognition are small.

To the best of our knowledge, the present prospective study was the first to compare the long-term effects of different invasive revascularisation methods (CEA, CAS) and BMT on patients' cognitive performance. Results of several studies describing cognitive changes after treatment are consistent with our findings and suggest a trend towards better verbal memory, attention and cognitive speed after CAS [31–33] or CEA [34], in particular in symptomatic patients [35, 36]. A possible explanation for improved cognitive performance after treatment of carotid artery disease is the amelioration of haemodynamic pathology and reduction of embolism. Perfusion restoration due to CEA, CAS or BMT could improve cognitive dysfunction caused by a state of chronic hypoperfusion before treatment [37]. A study combining perfusion variables and cognitive scores suggested that improvement of blood flow in the middle cerebral artery is associated with greater cognitive improvement in attention and executive functioning [38].

However, other studies suggest stable cognitive performance after intervention [6, 7, 11] or even a decline of cognition following CEA [4]. Over the past two decades, pharmacological management of cardiovascular disease and the efficacy of therapy have improved. Therefore, when comparing studies about the treatment effects of carotid artery disease, results of older studies must be interpreted with caution.

Comparison of CEA and CAS showed that CEA was associated with longer periods of ipsilateral carotid flow arrest compared with balloon inflations used during CAS [39]. On the other hand, CAS showed a higher frequency of microembolism [40] and higher rates of new ischaemic lesions [41]. The present data suggest that treatment method does not influence cognitive outcome. We conclude that transient blood flow arrest, despite the increased likelihood of new ischaemic lesions, is not detrimental to long-term cognitive function.

Variable study results are likely due to methodological differences such as absence of a control group, timing of cognitive testing with regard to recent symptoms and interventions, use of general anaesthesia during intervention, age of patients or differences in the follow-up time between treatment and assessment. Higher age of patients (>68 years) is suggested to be associated with a greater, more persistent decline of cognitive functions after CEA than after CAS [42]. Short intervals between pre-treatment and post-treatment cognitive assessment may not be sufficient to detect cognitive changes, in particular when effects of general anaesthesia and neurological or psychological factors are considered [5]. Furthermore, the motivation to undergo cognitive assessment immediately after treatment is expected to be lower than at a follow-up assessment. Hence, cognitive scores collected in the first few days after treatment may not reliably reflect cognitive performance level. Indeed, studies with short test-retest time intervals (days to months) generally found a decline or no change in cognitive performance after treatment [5, 43, 44]. In our study, mean time between treatment and assessment was about one year and we did not find an influence of time on cognitive change after treatment.

When interpreting the present study results, it has to be considered that new but clinically silent ischaemic lesions after CEA or CAS could lead to additional cognitive impairment [45]. However, a recent study found no association between the numbers of new lesions on diffusion weighted imaging and cognitive performance after 6 weeks or 3 months of follow-up [33]. The clinical significance of new ischaemic lesions on early diffusion weighted imaging can be questioned because of the partial reversibility of lesions. In addition, most lesions may be too small to cause cognitive impairment.

Our study participants were generally free of severe cognitive impairments. The homogeneity of the treatment groups, in particular the homogeneity of the symptomatic and asymptomatic patients with carotid artery disease, was confirmed by MRI (table 1). Still, patients with lower cognitive performance and worse emotional state before treatment benefited most from treatment, independent of treatment type. These results highlight the functional plasticity of the adult brain, even among patients with circumscribed morphological brain lesions due to carotid artery disease.

The lack of a perfusion measure is a limitation of the present study. Furthermore, time between treatment and follow-up was rather long and, hence, cognitive changes occurring immediately after treatment might not have been

Table 4: Gain scores across the treatment groups.

	BMT	CAS	CEA	*H*(2)/(p-value)
Interference control	–0.093*	–0.071	–0.017	0.40 (0.82)
Processing speed	0.042	–0.072	0.167*	2.74 (0.25)
Verbal fluency	0.088	0.053	0.163	1.10 (0.58)
Word production	0.000	0.000	0.033	0.30 (0.86)
Verbal learning	–0.009	0.079	–0.028	2.29 (0.32)
Verbal recognition	0.000	0.035*	0.000	0.66 (0.72)
Verbal recall	0.000	0.056	0.097	1.72 (0.42)
Short term memory	0.083*	0.083*	0.000*	0.33 (0.85)
Visual learning	–0.027	0.000	0.177	2.03 (0.36)
Visual recognition	0.000	0.000	0.000	1.41 (0.49)
Visual recall	0.000	0.000	0.222	0.69 (0.71)
Visual Rey immediate recall	0.039	0.191*	0.160	0.78 (0.68)
Visual Rey late recall	0.152*	0.269*	0.148	1.16 (0.56)

BMT = best medical treatment; CAS = carotid artery stenting; CEA = carotid endarterectomy
Data are median gain scores
* Indicates a significant improvement between first and second assessment (p <00.05)

detected. Following minor stroke or TIA, patients classified as asymptomatic are not always truly asymptomatic; they are still likely to show mild neurological symptoms. A control group would strengthen the study results, as possible practice effects and spontaneous improvement could be controlled for. However, a parallel version of the tasks was used whenever possible.

In conclusion, treatment of carotid artery stenosis improves long-term cognitive performance, independent of treatment type. With the progressive ageing of the population, the burden of cognitive impairment becomes increasingly important. It is therefore crucial to recognise cognitive improvement after treatment of carotid artery disease when estimating the risks and benefits of different reperfusion methods such as CEA, CAS or BMT.

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