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The Neurological Morbidity of Carotid Revascularisation: Using Markers of Cellular Brain Injury to Compare CEA and CAS

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Aim. *This comparative study attempts to evaluate the profile of S-100β and Neuron-Specific Enolase (NSE), biomarkers of brain injury, in patients undergoing carotid endarterectomy (CEA) and carotid artery stenting (CAS) and to correlate this with haemodynamic and embolic events detected using trans-cranial Doppler (TCD).*
Methods. *52 patients with internal carotid artery stenosis requiring intervention were recruited. 24 patients underwent CAS, and 28 underwent CEA. TCD was performed peri-operatively to record mean Middle Cerebral Artery (MCA) velocity and number of High Intensity Transient Signals (HITS) in the MCA of the operated side. Serum was drawn pre-operatively and at six time points in a 48 hour post-operative period, and then assayed using automated commercial equipment. Within and between group variability in markers were assessed by Generalized Estimation Equations modelling.*
Results. *CAS caused more HITS ($p = 0.028$) but less haemodynamic disturbance ($p = 0.0001$) than CEA. Treatment modality (CAS versus CEA) had no direct effect on S-100 changes ($p = 0.467$). NSE levels declined after revascularisation in the CAS group but not after CEA ($p = 0.002$). S-100β levels rose in patients who had higher numbers of HITS ($p = 0.002$). S-100β and NSE were not associated with changes in MCA velocity ($p > 0.5$). S-100β alone increased significantly at 24 hours in those patients with a post-operative neurological deficit ($p = 0.015$).*
Conclusions. *Trans-cranial Doppler findings suggest that the mechanisms of rise in S-100β and NSE levels may differ and may be due to increased peri-operative micro-embolisation and cerebral hypoperfusion respectively. Further studies are required to assess the clinical significance of these observed changes.*
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Keywords: Biomarker; Brain injury; Carotid surgery; Carotid stenting; Trans-Cranial Doppler.

Introduction

The current literature provides evidence-based indications for carotid endarterectomy (CEA) in both symptomatic and asymptomatic patients of low risk.[1–4] Results from other important studies in process are pending; the International Carotid Stenting Study (ICSS) and Carotid Revascularisation Endarterectomy versus Stent Trial (CREST) will provide the evidence for a more valid comparison between different carotid artery revascularization strategies.[5,6] For patients deemed 'higher risk', SAPPHIRE is the only randomized trial at the time of writing that provides clinical data.[7] However, meta-analysis of carotid angioplasty (some **without** stent placement) versus CEA has demonstrated that the 30-day stroke and death rates associated with CAS and CEA are not significantly different.[8]

Complication rates in terms of clinical stroke for both procedures have fallen since their inception, and are expected to fall further below figures recommended by those bodies supervising both techniques. As overt complication rates decline, it would be reasonable to question if there is any sub-clinical morbidity caused by CEA and CAS, with neurological injury being the most pertinent.

S-100β has been shown to be a sensitive marker of clinical and sub-clinical cerebral injury in a variety of clinical settings ranging from traumatic head injury and stroke, to post-operative neurological dysfunction in cardiac surgery patients.[9–11] S-100β is a cytosolic calcium-binding protein with the 'brain-specific' isoforms αβ and ββ predominantly present in astroglial and Schwann cells.[12] Maximum levels of S-100β can be detected as early as 20 minutes after brain injury,

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but it has a biological half-life of 30–113 minutes, and is rapidly excreted by the kidney.[13]

Serum Neuron-Specific Enolase (NSE) levels have been shown to correlate with infarct volume[14] and functional impairment after stroke.[15] In cardiac surgery, post-operative serum concentrations of NSE have a predictive value with respect to early neuropsychological and neuropsychometric outcome after cardiac surgery.[16] NSE belongs to a family of ubiquitous glycolytic enzymes occurring as series of dimeric isoenzymes including three subunits, the α, β, and γ chains.[17] The isoforms γγ and αγ are restricted to neurons. They have a molecular weight of 78 kDa[8] and a biologic half-life in serum of 20 hours.[18]

There are only limited data on the release of S-100β after CEA and CAS,[19] and none on that of NSE. No previous study has attempted to correlate changes in the levels of these markers with potential aetiological factors, such as peri-operative cerebral hypoperfusion or micro-embolic phenomena.

The aims of this study are the following: firstly to demonstrate the profile of S-100β and NSE release following CEA and CAS, and secondly to determine whether intra-operative haemodynamic events, measured using Trans-Cranial Doppler (TCD), are related.

Patients and Methods

The Local Ethics Research Committee gave a favourable opinion for the study. All patients gave informed, written consent prior to recruitment. Data were collected prospectively from patients considered for carotid revascularisation (CEA or CAS) between April 2005 and June 2006; patients were included consecutively. Exclusion criteria were combined open and endovascular surgery for revascularisation, need for general anaesthesia, and patient refusal to participate in the study. 40 (76.9%) patients were randomised (using ICSS criteria), the remaining 12 (23.1%) were selected for treatment according to patient and surgeon's preferences.

The degree of stenosis was determined using duplex ultrasonography and confirmed with CT angiography; the latter performed to assess patients' anatomical suitability for CAS in all cases, and to determine the degree of completeness of the circle of Willis. No patients in this series underwent preoperative intra-arterial angiography.

Carotid endarterectomy

CEA was performed under loco-regional cervical anaesthesia (50 mL 1% lidocaine) in all cases – as is our practice wherever practicable - by one of three Consultant vascular surgeons. Monitoring of physiological parameters and consciousness was conducted by a Consultant anaesthetist. Intra-arterial shunts were applied selectively; the decision being made pre-operatively (in cases where it was felt the Circle of Willis would not maintain adequate flow) or intra-operatively if the patient's conscious level decreased. Shunts were used in 3 (10.7%) cases. Dacron patch angioplasty of the ICA was performed in 75% of cases. Patients remained awake during the operation enabling active, clinical monitoring of their neurological state. Routine physiological monitoring included pulse oximetry, electrocardiogram, and invasive blood pressure measurement via the radial artery. Prior to clamping the ICA a dose of heparin (5000+/−2000 IU – depending on body weight) was injected intravenously.

Carotid artery stenting

CAS was also performed under local anaesthesia (20 mL 1% lidocaine) using access via the femoral artery in all cases. In most cases an 8F guiding catheter was used, having previously cannulated the external carotid artery. Heparin was administered to maintain an Activated Clotting Time (ACT) of 250–300 seconds. Similar supervision of the patients' physiological and neurological status was performed as for the CEA group. The procedures were performed by a team comprising a Consultant vascular surgeon, a Consultant radiologist, and a Consultant interventional cardiologist. Use of an Embolic Protection Device (EPD - filter-type) and dedicated carotid stenting system was universal.

Trans-Cranial doppler

On the day prior to the revascularisation procedure, patients underwent TCD monitoring using a Doppler-Box DWL C400 system (ScanMed Medical Instruments, UK) with a 2 mHz probe. Patients were rested at 45 degrees for a period of 15 minutes prior to scanning. Following initial examination of the intracerebral circulation to identify the MCA, a frame-mounted 2 mHz probe was positioned for the monitoring period (a standardised 30 minute period) to insonate the first part of the MCA through the temporal window. Emboli monitoring and MCA velocity recording was carried out 'on-line' by a single examiner. Using the recording facility on the TCD system, 'off-line' analysis by a blinded examiner could also be performed. These digitally-recorded images

were then examined by an experienced ultrasonographer (S.D.), with agreement in all recorded cases. A screenshot from the system showing two emboli and mean MCA velocity can be seen in Fig. 1.

Settings used were: depth 55(±5) mm, power 5–30 MW, and gain 5–20% to obtain the optimum display for emboli monitoring, the display of the spectral waveform within the window was optimised for each case, sample volume 10 mm, and a high pass filter was set at 50 Hz. Patients were scanned continuously for 30 minutes pre-operatively, and for the duration of their procedure (from positioning on the operating table through to transfer to the recovery area; CEA = 112 ± 24 minutes, CAS = 49 ± 15 minutes).

Emboli were counted manually. Criteria for the detection of emboli were established according to a previously published consensus statements.[20,21] Only unidirectional High-Intensity Transient Signals (HITS - less than 300 ms) at least 3dB higher than that of the background signal with a characteristic ''chirp'', ''snap'' or ''moan'' were recorded as emboli. A 3dB increase in decibel threshold was determined visually on the colour scale. When an 'embolic shower' (multiple HITS lasting longer than 1 second) occurred, 10 emboli per second were recorded. We acknowledge the limitations of this machine in the detection of emboli produced during CAS: The Fast Fourier Transform (FFT) has a time resolution of 10 milliseconds, and as such some short duration and high frequency HITS may have been missed during TCD monitoring.

At the time of cross-clamping or releasing the EPD in the ICA, the decrease in mean MCA velocity was calculated as the percent remaining velocity compared with the pre-clamping velocity, allowing a brief (10–15 s) period for cerebral autoregulation. These data were used in analysis of the biomarker results to further characterise and stratify the CEA and CAS groups. We were unable to determine the nature/composition of HITS using the software version we had available.

Serum biomarkers of brain injury

Pre-operative samples were collected in sodium citrate bottles from all patients via an arterial line strictly adhering to the schedule shown in Table 1. Samples taken at ≥48 hours were invariably taken from a peripheral vein as per our ethically-approved protocol.

Samples were subsequently centrifuged at 1800 rpm for 6 minutes at 20 °C and the resulting plasma stored in multiple aliquots at −80 °C; it was possible to complete this process within 15 minutes of collection for **all** samples as our laboratory is within 2 minutes of all clinical areas. Prior to analysis samples were defrosted in a water bath at 37 °C, visually checked for obvious

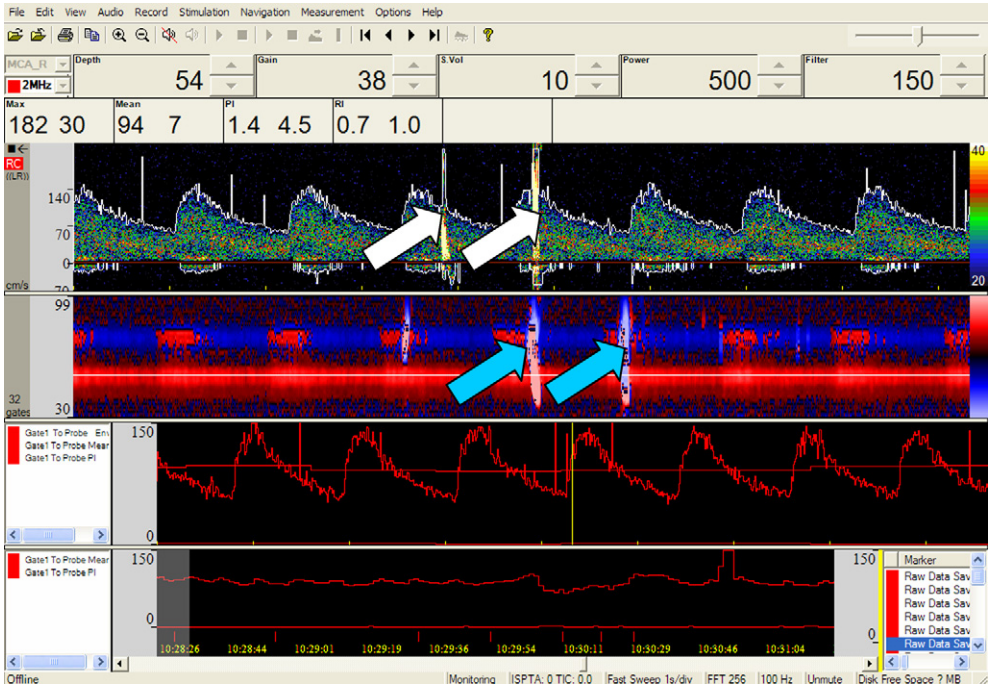

Fig. 1. Typical output from TCD – note real-time, mean MCA velocity of 94 cm/s and 2 HITS confirmed by audio (white arrows) then spectral (blue arrows) criteria.

Table 1. Schedule for blood sampling in both groups

Sampling Point	Operative Step
1	Pre-operatively in theatre
2	5 minutes post declamp/EPD retrieval
3	6 hours post operatively
4	12 hours post operatively
5	24 hours post operatively
6	>48 hours post operatively (if hospitalised)

haemolysis or hyperlipidaemia, and then immediately transferred to the automated analyser.

Serum levels of S-100β were determined using a commercially available, automated immunoluminometric assay (Liason® Sangtec® 100, DiaSorin S.p.A, Saluggia, Italy) with a lower detection limit of 0.02 μg/L and an upper limit of 30 μg/L. Upper limit of normal is 0.15 μg/L in 95% of adult population. NSE serum levels (normal upper limit 12.5 μg/L) were measured on the same analyser, using a similar methodology. The biochemist (R.S.) responsible for performing these analyses was blinded to the treatment group and TCD data.

Statistical analysis

Continuous variables were expressed as mean ± SD. P-values ≤ 0.05 were considered statistically significant. Comparisons of demographics, risk factors and TCD data between treatment groups were made using the *t*-test. Changes S-100β and NSE over time were considered as repeated measures data and analyzed by using Generalized Estimating Equations (GEE).[22,23] Marginal models (autoregressive matrix) based on generalised estimation equations were used to perform regression analysis. Our analysis took into account the fact that modelling the variation in markers of brain injury (S-100β and NSE) should be based primarily in subjects (within variation) rather than between different groups (between variation).

Regression analysis

We developed a GEE model and performed a multivariate regression analysis. The following variables were included: type of intervention (CEA or CAS), serum creatinine levels (only used in analysis of S-100β - which is cleared by the kidney), presence of a post-operative neurological deficit, timing of sample, high or low rates of embolisation (high > median number of HITS (58), low ≤ 58 HITS), and high or low drop in MCA velocity (high = MCA velocity drop > median (5%) from baseline, low = MCA velocity drop ≤5% from baseline).

Analysis was conducted by using the statistical software Intercooled Stata version 9.2 for Windows (Stata Corporation, USA) and SPSS version 15.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Descriptive results of study population

52 patients undergoing elective procedures were entered into this study (CEA = 28, CAS = 24). There were no statistical differences in terms of pre-operative symptom-status, or degree of stenosis (Table 2). There was a stronger history of IHD in the CAS group: this is to be expected through surgeon selection bias − CAS is most beneficial in reducing peri-operative MI risk. CAS was also performed in patients with a greater contralateral ICA stenosis, reflecting the inclusion of 2 patients with occluded contralateral vessels undergoing CAS prior to CABG (to safeguard their brain during periods of intra-operative hypotension).

Of those undergoing CEA, 2 (7.1%) patients had post-operative cranial nerve lesions (temporary) and 3 (10.7%) had clinically-apparent neurological deficits in the immediate (<24 h) post-operative period. There was one case of facial weakness (Modified Rankin Score[24] 1), one case of transient arm weakness (MRS 1), and one case of transient hemiparesis (MRS 3, but resolved completely). There were no new infarcts localised on post-operative CT imaging of the brain. There was no mortality at 30 days.

3 (13%) of those patients who underwent CAS had complications. 2 (8.7%) had haematomas at access sites (they did not require surgical exploration/repair), and 1 (4.3%) suffered a permanent ocular stroke on the operated side. No mortality was observed in the 30-day post-operative period, but two patients died before outpatient follow-up at 6 weeks: One from complications of valvular heart surgery, and the other from an acute myocardial infarction at home.

Trans-Cranial doppler studies

A trans-cranial ultrasonic window allowed capture of data in 20 (71.4%) of patients undergoing CEA and 18 (75.0%) of the patients who had CAS. This relatively low capture rate a result of either the patient having no acoustic window (9 patients - 17%) or the TCD resource not being available (6 cases - 11%). CEA was associated with a greater fall in MCA velocity (−25.5% Vs +2.7%, $p < 0.0001$) when comparing the

Table 2. Demographic and risk factor data for each treatment group

Variable	Carotid Endarterectomy		Carotid Artery Stenting		*p* value
	$N = 28$	%	$N = 24$	%	
Age (years)	67.2 ± 15.6	–	62.8 ± 19.3	–	ns
Male gender	17	60.7	20	83.3	ns
Symptomatic	19	67.9	10	41.6	ns
Asymptomatic	9	32.1	14	58.4	ns
Ipsilateral stenosis (%)*	79.4	–	82.0	–	ns
Contralateral stenosis (%)*	40.6	–	57.5	–	$p = 0.034$
History of hypertension	25	89.3	21	87.5	ns
History of smoking	16	57.1	18	75.0	ns
History of dyslipidaemia	23	82.1	24	100	ns
History of diabetes mellitus (IDDM or NIDDM)	7	25	7	29.2	ns
History of IHD (Previous angina/MI/CABG/PCI)	10	35.7	19	79.2	$P < 0.05$
Renal impairment	4	14.3	5	20.8	ns
COAD	6	21.4	8	33.3	ns

* Defined using Duplex scanning and ECST criteria.

period of ICA cross-clamping and the period that the EPD was deployed (Fig. 2). The duration of this interruption to normal flow in the operated ICA was also greater in the CEA group (41.5 minutes Vs 17.5 minutes, $p < 0.0001$) and this is demonstrated in Fig. 3.

There was excellent inter-observer reliability ($R^2 = 0.98$, $p < 0.01$), as demonstrated in Fig. 4. A mean of both observers' results was used to compare the incidence of HITS in both groups. We noted that CAS produced a significantly higher number of signals than CEA (239 Vs 42, $p = 0.028$) and this is shown in Fig. 5.

Serum biomarkers of brain injury

Baseline S-100β levels were 2–3 times higher than that of a normal population: Mean levels in the CEA group were 0.32 ng/mL (±0.33) and in the CAS group 0.52 ng/mL (±0.85). After intervention there was a non-significant trend of transient rise of S-100β levels in the group that underwent treatment with CAS: Levels in the CEA group appear unchanged. These results are shown in Fig. 6.

Baseline NSE levels were the same for each group (but at levels six times that of a normal population), and appeared to rise at 48 hours post-operatively in the CEA group, and decline in the CAS group. No statistically significant differences occurred between the treatment groups at any time point,– see Fig. 7.

Regression analysis

The results of these analyses are shown in Table 3. Changes in S-100β were not due to an effect of CAS

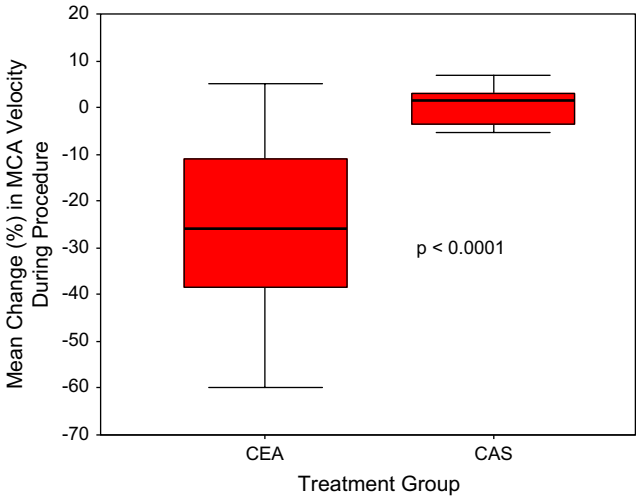

Fig. 2. Changes in mean MCA velocity (expressed as per cent change from pre-clamp/pre-EPD deployment values) for both groups.

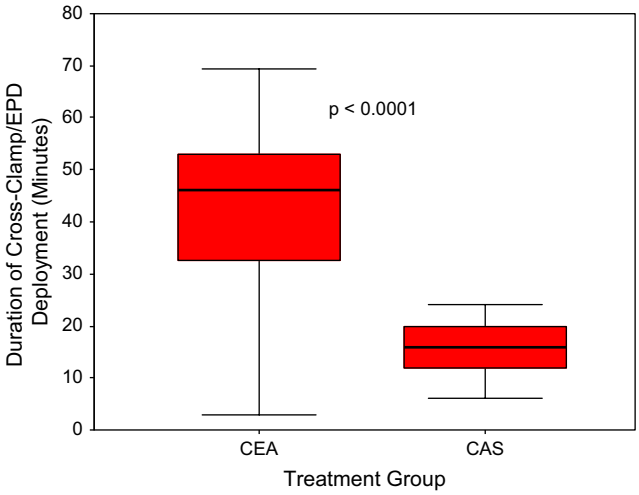

Fig. 3. Differences in duration of ICA cross-clamp and EPD deployment.

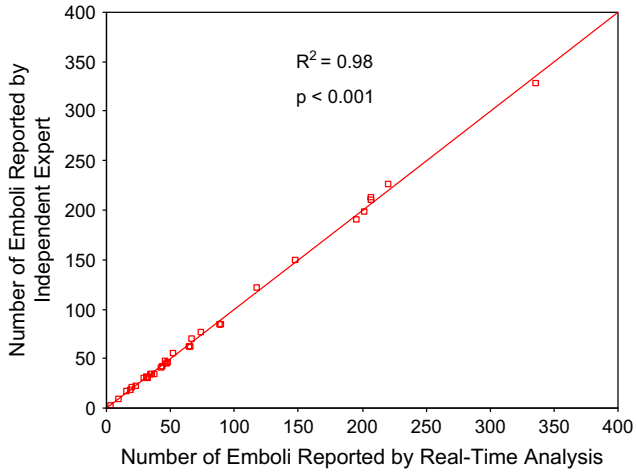

Fig. 4. Inter-observer reliability between real-time and off-line analysis of HITS was excellent.

versus CEA as a treatment modality for ICA stenosis ($p = 0.467$). CAS was responsible for a significant decrease in post-operative NSE levels when compared with CEA, ($p = 0.002$). Higher rates of embolisation were significantly implicated in changes of S-100β ($p = 0.002$), but not NSE ($p > 0.05$).

We saw no significant differences in S-100β levels in the groups that did or did not have drops in intra-operative MCA velocity, and within our models differences in NSE were not associated with changes in MCA velocity as measured using TCD ($p > 0.3$ in both instances).

In the group of patients that developed post-operative neurological complications there was a significant rise in S-100β levels compared to pre-operative levels ($p = 0.015$), but this was not complemented by a similar change in expression of NSE ($p = 0.467$).

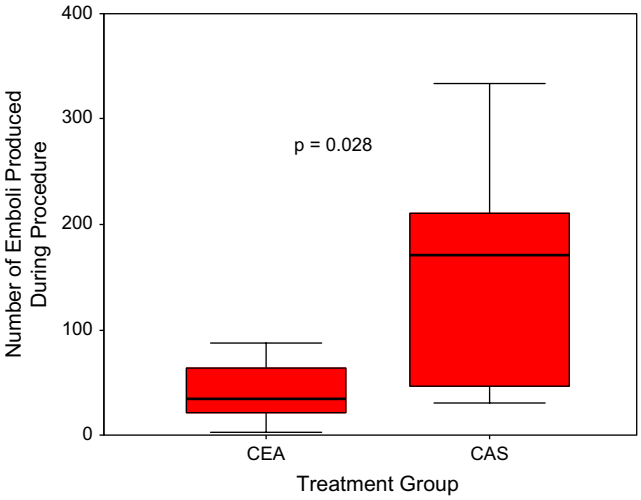

Fig. 5. Differences in the number of HITS recorded in each treatment group.

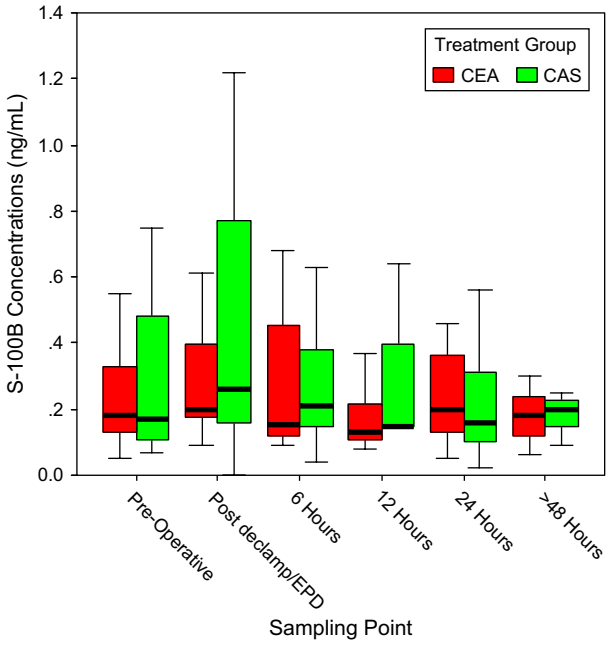

Fig. 6. Changes in S-100β for each treatment group over time. Note the non-significant increase in mean concentrations for the CAS group at the post-EPD retrieval and 6 hour time points.

Discussion

Our data strongly suggest that the number of HITS detected using TCD during carotid revascularisation is related to the observed changes in levels of

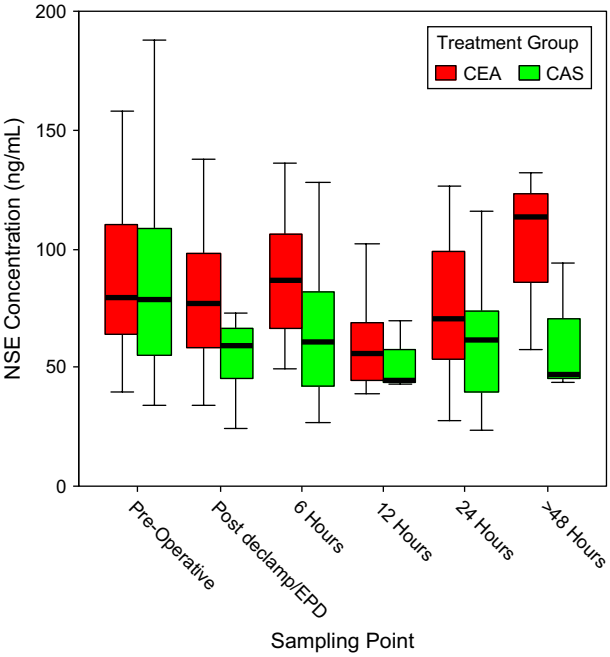

Fig. 7. There was a trend for NSE serum levels to decline after treatment in the CAS group, and rise in the CEA group.

Table 3. Results of GEE using models for both S-100β and NSE

	b-coefficient	Standard error	*p*-value	95% CI
S-100β				
Effect of CAS Vs CEA	−0.067	0.092	0.467	−0.25 to 0.11
Creatinine	−0.001	0.001	0.472	0.09 to 0.37
Timing of sample	0.054	0.054	**0.008**	0.01 to 0.09
Post-op deficit	0.182	0.074	**0.015**	0.04 to 0.33
MCA Velocity Drop	1.023	8.345	0.324	−26.56 to 18.43
HITS	0.231	0.073	**0.002**	0.09 to 0.37
Constant	0.057	0.127	0.655	−0.19 to 0.31
NSE				
Effect of CAS Vs CEA	−34.429	11.249	**0.002**	−56.48 to −12.38
Timing of Sample	4.537	2.319	**0.050**	−0.01 to 9.08
Post-op deficit	6.686	9.183	0.467	−11.31 to 24.68
MCA velocity drop	−2.439	10.299	0.813	−22.63 to 17.75
HITS	0.187	12.911	0.654	−0.12 to 2.12
Constant	56.953	20.610	0.006	16.56 to 97.35

S-100β; a serum marker of brain injury that has been shown to correlate with long-term neurological outcome after cardiac surgery.[11] Our observations have shown CAS is associated with higher numbers of peri-operative HITS than CEA (despite using a cerebral protection device routinely) but we were unable to show any statistically significant changes in S-100β when comparing both treatment groups. It is however important to note a non-statistically significant trend for mean S-100β concentrations in patients undergoing CAS to increase, while mean levels remained static throughout the measured time course in those undergoing CEA. This finding is contradictory to the results of the one previously published study that compared S-100β levels in only 14 cases of CAS, and 28 of CEA.[19] There are two possible explanations: Firstly in the latter series patients routinely received a general anaesthetic (GA) for CEA which could be a confounding factor, and secondly the statistical methodology used to assess repeated measures in this instance was, however, less sensitive than that employed in our study.

It has been previously hypothesised that the rise in S-100β observed in patients undergoing CEA is due to a transient impairment of the blood-brain barrier, or even represents sub-clinical neurological injury associated with brain cell death. The postulated aetiology of this 'injury' is hemispheric hypoperfusion, leading to global ischaemia. The findings from our TCD studies have confirmed that CEA generates more flow disturbance (in terms of MCA velocity reduction) than CAS. During CAS hypoperfusion is limited by the use of an EPD that allows continuous antegrade flow of blood in the operated ICA. Also, the use of a balloon (that occludes flow in the ICA) to perform a pre-dilatation angioplasty or expand a stent is temporary, lasting 5−10 seconds.

It is also important to identify the reasons why we observe an S-100β rise in the CAS group. There are several explanations for this: Firstly, an increased number of HITS (and thus assumed embolic phenomena) observed during carotid revascularisation is potentially more injurious (in terms of S-100β increase only) than a period of relative hypoperfusion, especially if patients have been 'preconditioned' to hypoperfusion by having a haemodynamically significant ICA stenosis and/or a previous ischaemic injury to the brain (i.e. TIA or stroke); this argument can be strengthened by our observation of higher levels of S-100β in the group with greater levels of embolisation. Secondly, by using awake neurological monitoring during CEA we have been able to place a shunt in those patients who may otherwise have had an S-100β rise without a recognisable physiological response suggestive of brain ischaemia (e.g. hypertension after ICA cross-clamping). Finally, other factors should be considered, but are difficult to investigate: Completeness of the Circle of Willis (CoW), plus the degree of external-internal carotid communication/collateralisation must be important and both warrant further investigation.

Levels of NSE behaved differently; it was not related to TCD-detected changes in MCA velocity, number of detected HITS, nor post-operative neurological deficit. Instead we noted the significant effect of NSE levels declining after revascularisation, but less so after CEA compared with CAS. This trend has been previously described before by Rasmussen *et al.* who noted that patients undergoing CEA had higher preoperative levels of NSE than a control group (matched for age and risk factors but without significant, concurrent ICA stenosis) undergoing abdominal aortic aneurysm (AAA) repair, and that after treatment NSE levels lowered post-operatively to the level

observed in the AAA group.[25] We currently have no robust explanation for this observation, but we may hypothesise that a significant ICA stenosis causes a higher background level of NSE release, and on overcoming such haemodynamically significant lesions brain perfusion is normalised and these levels subsequently fall with time. Of note, we observed a non-significant trend for pre-operative NSE levels to be higher in patients with greater degrees of bilateral ICA stenosis and to rise in patients who had very large drops in their MCA velocity during their revascularisation procedure (i.e. those who underwent ICA cross-clamping and had a deficient CoW). This raises important questions as to the aetiology of injury (e.g. embolisation versus global ischaemia, or a combination of both) that causes NSE, and indeed S-100β, to be released.

We observed high *pre-operative* levels of S-100β in both treatment groups, with highest levels in the CAS group particularly. This overall observation could be representative of the number of recently symptomatic (and therefore recently brain injured) patients in our study population, but we cannot explain the disparity in baseline levels of S-100β between treatment groups. We also noted that those patients who produced a greater number of HITS (thus emboli) during their procedure had higher baseline levels if S-100β than those that did not.

3 patients suffered from a neurological deficit after CEA and one suffered an ocular stroke after CAS. The peak concentration of S-100β occurred near 24 hours after injury and this is in keeping with other studies looking at its release in patients with such deficits and validates our results: Sustained elevated S-100β levels correlate with neurological complications, and the amount released tends to reflect the extent of ischaemic damage to astro-glial cells.[26]

Study limitations

Potential criticisms of the study could include that the samples taken within the first 24 hours were from an arterial line, and subsequent samples from a venous site. While small differences in S-100β serum levels in samples taken simultaneously from the radial artery and a jugular line has been shown, others have shown no difference.[27] We must also accept that the study population was not fully randomised and that surgeon/patient choice may have created a selection bias: fortunately, however, this did not cause significant differences when comparing the degree of stenosis and comorbidity between treatment groups. Continuing TCD monitoring in the post-operative period for a period longer than 15 minutes would also have been beneficial, since many HITS may have occurred undetected during this period. Finally a more sensitive marker of renal function and impairment, such as Cystatin-C, may have shown differences between each treatment group and impacted more on subsequent regression analyses.

Our group continues to study the sub-clinical neurological effects of CEA and CAS using other outcome measures including neuropsychometric testing, high-resolution neuro-imaging techniques, and novel serum markers of brain injury. We are also studying the effects of degrees of completeness of the CoW, and extent of extra-intra cerebral collateralisation on such outcomes.

In determining the clinical relevance of these findings by using such morphological and functional techniques we hope to be able to better predict which patients are at risk of clinical and sub-clinical neurological injury, and to be able to decide whether open or endovascular treatment is safer on a patient-to-patient basis. This will allow us to offer a more individualized option for the management of atherosclerotic ICA stenosis (e.g. CEA or CAS, type of EPD and stent, prophylactic shunt) and thus improve patient safety and outcome.

Conclusions

The present study suggests that an increased incidence of HITS during carotid revascularisation may be responsible for either a transient defect in BBB function, or cause actual brain cell damage/death. This is despite routine use of an EPD that allows continuous antegrade blood flow routinely for CAS, and awake monitoring during CEA. Although embolisation appears to be more frequent during CAS, more clinical neurological complications occurred in the group undergoing CEA, in whom we saw greater MCA flow disturbance. This raises the question of the clinical significance of transient rises in S-100β and NSE, such as that measured in most of the patients we studied, and is the subject of further investigation by our group.

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