



Jugular Venous Neurone Specific Enolase (NSE) Increases Following Carotid Endarterectomy Under General, but Not Local, Anaesthesia

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Submitted 19 January 2009; accepted 13 May 2009

Available online 21 June 2009

KEYWORDS

Carotid
endarterectomy;
Anaesthesia;
Neurone specific
enolase;
S-100B

Abstract *Introduction:* Previous studies indicate that local (LA) rather than general anaesthesia (GA) for carotid endarterectomy (CEA) is associated with reflex hypertension and preservation of cerebral cytochrome oxidase after carotid clamping. The hypothesis that LA offers protection against ischaemic cerebral injury has been investigated by measuring ipsilateral jugular venous neurone specific enolase (NSE: neuronal glycolytic enzyme) and S-100B (glial cell protein) during and after CEA.

Methods: 27 patients with symptomatic carotid artery disease (70–99% stenosis) underwent CEA, 14 under LA and 13 under GA. Jugular venous blood samples were assayed for NSE and S-100B before carotid clamping and at 5 min before and 5 min, 2, 4, 6, 8, 12 and 24 h after clamp release.

Results: No neurological complications occurred. S-100B levels were low and did not increase from baseline in either group. Pre-clamp NSE levels were similar in both groups (LA: 17.6 (15.2–20.7) µg/l, GA: 21.5 (11.3–26.2) µg/l; $p = 0.37$) but increased significantly 2 h after clamp release in GA patients (LA: 25.5 (16.6–27.8) µg/l, GA: 48.2 (31.4–61.3) µg/l, $p = 0.05$) with a significant rise from baseline in GA patients ($p = 0.04$).

Conclusions: CEA performed under GA is associated with greater rises in jugular venous NSE, and hence cerebral injury, than CEA performed under LA.

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Introduction

Although carotid endarterectomy (CEA) reduces the long term risk of ischaemic stroke surgery may be complicated by acute cerebral ischaemia.^{1,2} Its benefit depends on a low complication rate and thus procedural modifications that minimise ischaemic injury might be beneficial. In this respect previous studies using near infrared spectroscopy

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have shown better preservation of cerebral oxygenation, cytochrome oxidase levels and perfusion during surgery under local anaesthesia (LA) compared with general anaesthesia (GA).³ These potential benefits were associated with a significant rise in systemic blood pressure in LA patients following carotid clamping. However there are no studies which examine the degree of cerebral injury associated with different anaesthetic techniques.

One difficulty in assessing acute cerebral ischaemic injury is the wide spectrum of changes that may occur, varying from a clinically obvious stroke to subtle neuropsychological dysfunction. Thus, Vanninen et al.⁴ demonstrated a deterioration in cognitive function in 63% of patients one month after CEA with only 5% demonstrating an overt neurological deficit. Further, the neuropsychological tests that quantify these effects may be unreliable or difficult to interpretate because of the influence of general health status, anxiety and practice on the results.⁵ More recently, specific brain-derived proteins such as S-100B or neurone specific enolase (NSE) have been proposed as neuro-biochemical markers of adverse neurological outcome.⁶ In a rat model of middle cerebral artery occlusion a significant increase in circulating NSE levels occurred 2 h after a focal ischaemic insult.⁷ Similarly serum levels of these markers correlate with adverse neurological outcomes after traumatic brain injury,⁸ cardiopulmonary bypass⁹ and stroke.¹⁰ This affords an opportunity for objective quantification of cerebral injury during CEA.

Despite these studies systemic NSE and S-100B levels in patients undergoing CEA have failed to reflect clinical outcome unless there was an obvious neurological deficit rather than cognitive impairment.^{11–13} This could be explained on the basis that isolated cognitive impairment is a manifestation of minimal cerebral damage which may be associated with lower and possibly transient increases in serum markers that are undetectable in peripheral blood samples.¹⁴ The hypothesis that LA offers greater protection against ischaemic cerebral injury has thus been investigated by measuring ipsilateral jugular venous NSE and S-100B levels during and up to 24 h after CEA.

Methods

Patients

During 2001 27 consecutive patients were randomised as part of the GALA Trial¹⁵ to undergo carotid endarterectomy under general ($n = 13$) or local anaesthesia ($n = 14$). The two groups were similar in terms of age, sex and the presence of cardiovascular risk factors (Table 1). All had a 70–99% ipsilateral symptomatic carotid stenosis (mean stenosis 80% for both groups) as assessed by colour flow duplex ultrasound (Acuson 128XP, California, USA), with moderate narrowing of the contralateral internal carotid artery (GA group average 30%, LA group average 40%). Details of symptoms occurring during the preceding 6 months are shown in Table 2.

Anaesthesia

All patients received midazolam 2 mg iv either prior to induction of general anaesthesia or administration of the

Table 1 Clinical details of patients undergoing carotid endarterectomy

	GA (13)	LA (14)	<i>p</i>
Age ($\pm$ iqr)	67 (54–76)	68 (51–77)	0.77
Male	8	8	1.00
Hypertension	13	12	0.50
Diabetes Mellitus	3	4	1.00
Hyperlipidaemia	11	11	1.00
Current smoking	4	4	1.00
Aspirin	13	14	1.00
Anticoagulants	0	0	—

local anaesthetic nerve block. Loco-regional anaesthesia was achieved by a standard superficial cervical plexus block using 20 ml 0.25% bupivacaine and 1/200000 adrenaline. General anaesthesia was induced with fentanyl and vecuronium, and maintained on a mixture of isoflurane (0.6–1%), nitrous oxide (60%) and oxygen (40%). In those patients receiving a GA, systemic blood pressure was adjusted using an epinephrine infusion if it fell below the preoperative blood pressure.

Surgery

A standard endarterectomy technique was used in all patients. The carotid sinus was anaesthetised with 2 ml 1% lignocaine before full dissection of the carotid vessels. The external, internal and common carotid arteries were clamped sequentially and a longitudinal arteriotomy and endarterectomy performed. Distal tacking sutures were inserted when necessary with routine closure of the arteriotomy with a Dacron patch.

Monitoring

Patients were monitored with intra-arterial blood pressure, pulse oximetry and electrocardiography. Mean stump pressure was measured in all patients and those receiving local anaesthesia were subjected to awake neurological testing during cross clamping (squeezing a squeaky toy held in the contralateral hand, move the contralateral lower limb, perform simple mental arithmetic, to recite their address, engage in regular conversation).

Shunting

Patients who received a GA were shunted if the mean stump pressure was <50 mm Hg. The primary indication for shunt insertion in LA patients was deterioration in cerebral function or the level of consciousness as assessed by awake neurological testing.

Jugular venous sampling

The ipsilateral internal jugular vein was cannulated under direct vision prior to carotid clamping and the tip of the catheter (Vygon Leadercath: Vygon, Cirencester, UK) placed in the jugular bulb. This remained *in situ* for 24 h. Blood samples (5 ml) were obtained before carotid clamping, and 5 min before and 5 min, 2, 4, 6, 8, 12 and 24 h after clamp release. Samples were placed in tubes without anticoagulant. Blood was allowed to clot and after centrifugation (1000g for 10 min), separated serum was stored at -80°C for later analysis.

Table 2 Details of carotid symptoms, stenosis and surgical technique

	GA (13)	LA (14)	<i>p</i>
Symptom	AF:3, CVA:4, TIA:7	AF:2, CVA:4, TIA:7	0.74
Last event, weeks	13 (6–20)	12 (6–20)	0.72
Ipsilateral stenosis, %	80 (75–90)	80 (75–90)	0.78
Contralateral stenosis, %	30 (20–50)	40 (20–50)	0.74
Contralateral occlusion	1	1	1.00
Abnormal vertebral flow	0	0	–
Carotid clamp time, min	48 (40–60)	50 (40–65)	0.78
Stump pressure, mm Hg	49.1 (39–84)	48.5 (37–81)	0.73
Shunt	8	1	0.01
Patch	13	14	1.00

AF – Amaurosis fugax, CVA – stroke, TIA – transient ischaemic attack, Data = median $\pm$ iqr.

NSE and S-100B assays

Serum NSE and S-100B levels were measured (blind to anaesthetic method) using an immuno-luminometric assay and a fully automated LIA-mat system (AB Sangtec Medical, Bromma, Sweden). Sangtec 100 measures the β -subunit of S-100B as defined by 3 monoclonal antibodies. NSE was measured using monoclonal antibodies that bind to the γ -subunit of the enzyme.

Clinical outcome

A standard neurological examination was performed 24 h after surgery and prior to discharge from hospital.

The hospital research ethics committee approved this project.

Statistical analysis

Significance of observed changes from baseline and between different time points within each group was tested with ANOVA and paired *t* tests. Numerical data between groups were compared using the Mann–Whitney *U* test because of a “non-Gaussian” distribution and small sample size. Categorical data was compared by the Fisher exact test.

Results

No neurological complication occurred in these patients.

S-100B levels were low and did not change from baseline levels in either group [baseline levels GA: 0.10 μ g/l (0.08–0.11), LA: 0.13 μ g/l (0.12–0.17) [Fig. 1].

Pre-clamp NSE levels were similar in both groups [LA: 17.6 μ g/l (15.2–20.7), GA: 21.5 μ g/l (11.3–26.2); *p* = 0.37]. Peak levels occurred 2 h after clamp removal and were significantly higher in GA patients [LA: 25.5 μ g/l (16.6–27.8), GA: 48.2 μ g/l (31.4–61.3), *p* = 0.05, Mann–Whitney]. At 2 h, the increase from baseline in the GA patients was significant (*p* = 0.04) and NSE levels remained elevated in GA patients at all time points up to 12 h, returning to baseline at 24 h (Fig. 2).

Discussion

This study is the first to compare S-100B and NSE levels in patients undergoing CEA with either LA or GA. It is also one of a minority that has measured these potential markers of cerebral injury in the jugular vein, rather than systemic venous blood, throughout the study period. Thus the results should more accurately define any changes that occur.

Clearly there was no difference in baseline NSE and S-100B levels (pre-clamping) between GA or LA patients. This remained the case during carotid clamping. Further, although some reports have described a small but significant increase in S-100B during clamping^{13,16} this did not occur in the present study, a finding that concurs with several others reports in patients undergoing uncomplicated GA^{12,14} or LA¹⁷ CEA. In contrast S-100B levels rise in patients who develop a significant neurological deficit following CEA or carotid angioplasty (CAS)^{12,13,18} and those with impaired neuropsychometric testing post-operatively.¹⁹

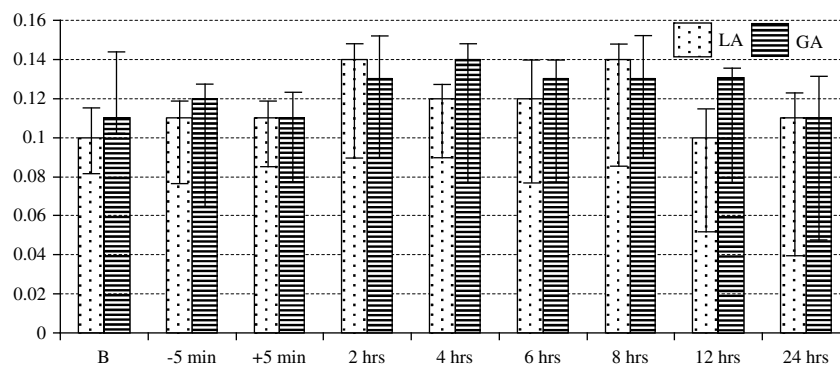


Figure 1 Jugular venous S-100B levels (μ g/l; median $\pm$ iqr) during and after carotid endarterectomy under local or general anaesthesia. Baseline levels (B): LA v GA, *p* = 0.8. Baseline to peak: LA *p* = 0.7; GA *p* = 0.8.

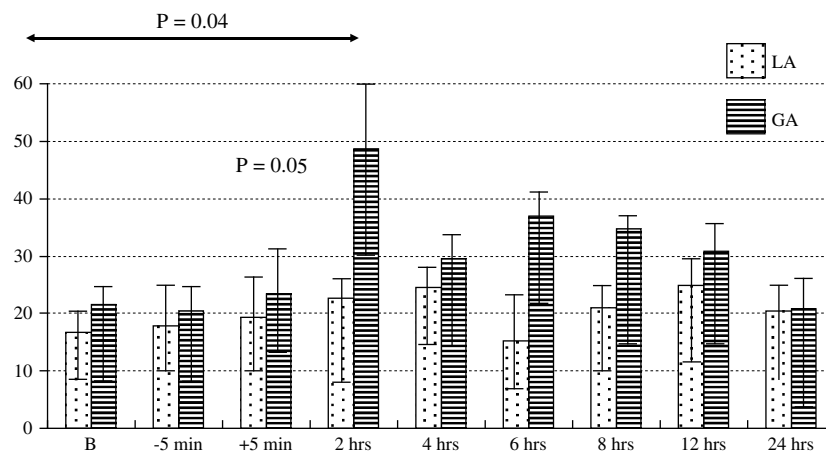


Figure 2 Jugular venous NSE levels (ug/l; median $\pm$ iqr) during and after carotid endarterectomy under local or general anaesthesia. Baseline levels: LA v GA, $p = 0.4$. Baseline to peak: LA $p = ns$; GA $p = 0.04$. LA v GA at 2 h post-op: $p = 0.05$.

Further, Brightwell et al.¹⁸ showed that patients with multiple embolic events during CAS also demonstrated elevated levels of this protein.

Following cerebral reperfusion NSE levels increased significantly in GA patients, peaking 2 h after carotid clamp release. They remained elevated for 12 h following clamp release (Fig. 2) and were significantly higher than in patients receiving LA.

Elevated serum NSE levels reflect ischaemia-induced cytoplasmic enzyme loss and are detectable before irreversible neuronal damage occurs. This rise in jugular venous NSE levels following CEA under GA would be consistent with previous work suggesting that LA better preserves cerebral oxygenation and perfusion compared to GA.³ Such an observation would support the concept that CEA under LA might be associated with lower peri-operative stroke and death rates. Whilst this is endorsed by a systematic review of non-randomised and randomised studies²⁰ the recently published GALA Trial¹⁵ has failed to confirm this benefit. In the latter stroke occurred in 4.0% (70/1752) of GA patients and 3.7% (66/1771) of the LA group. Although the outcome of such a large study might be expected to provide conclusive evidence on the possible benefit of CEA performed under LA, there were confounding factors. In particular intra-operative blood pressure was pharmacologically elevated in more GA patients (43% v 17%) thus mimicking the post-clamping reflex hypertension that is thought to be responsible for improved cerebral physiology in LA patients.

S-100B is a protein found primarily in cerebral glial cells and a rise in serum levels is specific to glial cell injury.⁶ The results of this study therefore suggest that neuronal rather than glial cell injury is more likely during CEA under GA reflecting the greater susceptibility of the neuronal cells to ischaemia. An alternative explanation for the different patterns of NSE and S-100B release may have been limiting venous sampling to 24 h post-operatively. In a previous study correlating neuro-behavioural outcome after stroke with serum S-100B, peak levels occurred on the second day post-stroke, whereas serum NSE levels were maximal on admission.¹⁰ This may reflect a delayed glial cell response to ischaemia.

A recent study by Brightwell et al.¹⁸ assessed systemic NSE levels after CEA under LA and compared them with NSE levels following carotid angioplasty and stenting (CAS). Surprisingly, these authors found that NSE increased 6 h post-CEA despite the avoidance of general anaesthesia. Nevertheless the peri-operative stroke rate was high (10.7%) and this may have distorted the results. Moreover, systemic rather than jugular venous sampling makes comparisons between the studies difficult, since systemic arterial and venous S-100B levels are lower than those measured in jugular venous blood.^{14,21}

Jugular rather than systemic venous blood was assayed to minimise dilutional effects and to obtain blood principally derived from the ipsilateral cerebral hemisphere. Although there is some mixing of venous blood from the two hemispheres in the sigmoid sinus in a steady state it can be assumed that the jugular venous drainage from a particular side reflects metabolism in the ipsilateral hemisphere. A similar technique has been used previously to assess cerebral oxygen extraction during CEA.^{22,23}

Whilst it might be suggested that an increase in these putative markers of cerebral injury following CEA under GA is due to possible extracerebral effects of anaesthesia, previous studies show no change in NSE levels following abdominal aortic aneurysm repair¹¹ or of S-100B after thyroidectomy.²⁴ Thus it is reasonable to assume that their source is exclusively cerebral and is not influenced by GA *per se*.

Currently there is increasing enthusiasm for carotid angioplasty and stenting as an alternative to carotid endarterectomy although there remains no good evidence to prefer this over surgery in patients with a symptomatic carotid stenosis. CAS is undoubtedly associated with more intra-procedure embolic events^{18,25} and these appear to be associated with higher S-100B levels, even in peripheral blood.¹⁸

In summary this study shows that an acute increase in jugular venous NSE levels is observed after CEA performed under GA, but not after CEA performed under LA. This is further evidence that during CEA, LA may provide some protection against peri-operative cerebral injury.

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