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NSE and Neurological Changes During Carotid Endarterectomy Performed in Awake Patients

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SUMMARY

Background: The aim of this pilot investigation was to determine if a raised serum NSE (neuron-specific enolase) level or a decrease in rSO_2 following carotid revascularization with CEA (carotid endarterectomy) could be used to detect neurological instability in CEA patients. We hypothesised that increased serum NSE levels during CEA would be linked to neurological symptoms after surgery.

Patients and Methods: A total of 64 consecutive CEAs were prospectively evaluated in 60 patients who underwent the procedure under LA (local anaesthesia) during an 18-month period. The cerebral oximeter was used to measure cerebral oxygen saturation (rSO_2) before and after cross-clamping, along with the serum concentration of NSE. Selective shunting was performed when neurological changes occurred, regardless of rSO_2.

Results: The neurological symptoms that occurred after clamping correlated with a less pronounced decrease in the serum level of NSE (P = .026) during the 12-hour timeframe after the procedure. The cut-off of 13.1% of NSE decrease was determined to be optimal for identifying patients with neurological symptoms. There was no correlation between rSO_2 decline and neurological symptoms (P = .675). Two (3.1%) perioperative strokes occurred.

Conclusion: Awake neuromonitoring has been found to be a sensitive and direct evaluation method for brain tissue perfusion and is specific to CEA under LA. Although there was a favourable correlation between CEA and a change in serum NSE, serum NSE monitoring was not practicable due to the paradoxical serum NSE decrease and late statistically significant change (12 hours after the procedure).

Keywords: Perioperative Stroke Prevention; Neuromonitoring; Carotid Stenosis; Selective Shunting

Abbreviations: CEA: Carotid Endarterectomy; ICA: Internal Carotid Artery; LA: Local Anaesthesia; GA: General Anaesthesia; NSE: (Neuron-Specific Enolase; TIA: Transient Ischaemic Attack; NPV: Negative Predictive Value; (LR+): Positive Likelihood Ratio; (LR-): Negative Likelihood Ratio; AUC: Area Under the Curve

Introduction

Carotid endarterectomy (CEA) is widely accepted as the appropriate procedure in patients with severe carotid artery stenosis to reduce subsequent ischaemic stroke. The inherent risk of surgery is perioperative stroke. A cause of cerebrovascular accidents could be the hypoperfusion during cross-clamping of the internal carotid artery (ICA). The prompt and reliable recognition of insufficient collateralisation is crucial for a good neurological outcome of patients [1]. The general use of an indwelling shunt adds to the complexity of CEA, and can injure the artery, leading to thromboemboli [2]. Therefore, proper neuromonitoring is needed to identify patients who will benefit from shunt placement [3]. Patients undergoing CEA under local anaesthesia (LA) are monitored clinically, which arguably results in a more appropriate shunt insertion compared with other less-sensitive methods of neuromonitoring [4]. Most patients are operated on under general anaesthesia (GA). They cannot be monitored clinically, so new options are being explored. Several biomarkers have been proposed to predict, diagnose, and monitor brain injury. Among the most studied of these is NSE (neuron-specific enolase) [5]. NSE is the neuronal form of the intracytoplasmic glycolytic enzyme enolase. It is a homodimer composed of γγ subunits with a molecular weight of 78,000 [6]. NSE is localized throughout the cytoplasm of neurons, including soma, axon, and dendrites, but not the nucleus [7].

It has a half-life in human serum of 24 hours [8]. Serum concentrations of NSE peak between 7 hours [9] and 2 days [10] after cerebral injury. Elevations in NSE concentrations correlate with infarct volume, although less convincingly than S100B protein (S100B) levels [10]. It is ambiguous whether NSE serum concentrations successfully predict functional outcome after stroke, with some studies finding a positive association [8] [9] and others failing to show a correlation [10]. Although the level of NSE is highly specific for brain tissue, it is also expressed in other cell types under certain physiological and pathological conditions, such as other neurological diseases, known malignancies, chronic inflammatory diseases, recent infection, or trauma [11]. Subclinical neurologic ischemic events can also be detected by measuring serum NSE [12] and are associated with short- and long-term neuropsychological outcomes after traumatic brain injury [13]. NSE is a molecule that has been extensively studied for its potential in the diagnosis and prognosis of stroke. However, high sensitivities and specificities reported in the scientific literature do not always correspond with the practical performance of these and other blood markers. Concentrations of NSE were found to be significantly higher in patients with stroke than in control subjects, while no differences were observed in transient ischaemic attack (TIA) and mimics. Levels of NSE and S100B were significantly correlated in stroke patients, but not in controls or in stroke mimics [11].

(Kuzhuget, et al. [14]) studied the role of stump pressure and cerebral oximetry in predicting ischaemic brain damage during CEA. He showed that temporary shutdown of blood flow during CEA was accompanied by a significant elevation of NSE concentration, which subsequently returned to normal levels three days after surgery. (Dragas, et al. [15]) found decreased NSE concentrations during conventional CEA with routine use of shunt and Dacron patch after declamping, while during eversion CEA without the use of shunt the NSE values slightly increased. On the other hand, (Palombo, et al. [16]) found that patients with and without shunt had similar serum concentrations of NSE. (Dragas, et al. [15]) added that routine shunting during surgery for symptomatic carotid stenosis may have the potential to prevent postoperative increase of serum NSE levels, which is a potential marker of brain injury. (Wijeyaratne, et al. [17]) showed that an acute increase in jugular venous NSE levels is observed after CEA performed under GA, but not after CEA performed under LA. This suggests that during CEA, LA may provide some protection against perioperative cerebral injury. (Brightwell, et al. [18]) found that the mechanisms behind the rise in NSE levels may be due to cerebral hypoperfusion. (Sahlein, et al. [6]) did not find any correlation between subtle cognitive decline after CEA and intraoperative levels of NSE. The aim of this preliminary study was to investigate whether increased serum levels of NSE or a drop in cerebral oximetry (rSO_2) are able to detect neurological instability in patients undergoing carotid revascularisation by CEA under LA. We hypothesised that increased serum levels of NSE would correlate with neurological symptoms during CEA.

Patients and Methods

Study Population

A prospective observational study design was performed with patients who underwent CEA. Sixty adults (41 men, 19 women) between the ages of 50 and 86 years who underwent 64 CEAs over a 12-month time period were studied. The approval of the National Medical Ethics Committee of the Republic of Slovenia was obtained, and written informed consent was obtained from all the patients. Indications for CEA included ipsilateral neurological symptoms (stroke, TIA, amaurosis fugax) with ≥50% ICA stenosis, and both symptomatic and asymptomatic patients with 70% to 99% stenosis.

Carotid Endarterectomy

Twenty-six patients were symptomatic, and all were scheduled to undergo CEA with LA achieved by the combination of superficial and deep cervical plexus block (100 mg levobupivacaine + 200 mg lidocaine). After carotid clamping, neurological assessment was performed by having the patient squeeze into the contralateral hand and speak. Neurological assessment was continuous throughout the operative procedure at 3-min intervals. The patients were assigned to one of two groups: those who developed neurological symptoms (neurological symptoms group) during clamping and those who did not (no neurological symptoms group). Criteria for the neurological symptoms group were the development of motor weakness, slurring of speech, inability to respond appropriately to verbal commands, loss of consciousness, or seizure. These were also used as criteria for insertion of a shunt or anticipating a very short clamp time with primary closure. Patch closure was performed in 58 CEAs, with primary closure in 6.

Cerebral Oximetry

The cerebral oximeter INVOS 5100C (Somanetics) was used to measure simultaneous, bilateral rSO_2 throughout the procedure. During surgery, brief and variable degrees of cerebral ischaemia occur during cross-clamping of the ICA [19,20]. The pre-clamping bilateral rSO_2 value and the lowest ipsilateral measurement after ICA clamp placement were recorded. Intersubject variability in rSO_2 index values is well known and was noticed in this study. To facilitate comparison of rSO_2 changes after carotid cross-clamp among all patients, and to determine the magnitude of rSO_2 change that was associated with a change in neurological function, the rSO_2 data were normalised by calculating a percentage change in rSO_2 reading during cross-clamp periods in each patient according to a formula (Figure 1). On the basis of previous studies [21], a decrease in rSO_2 of ≥12% was considered clinically significant.

$$Percentage\ change = \frac{mean\ rSO_2\ reading\ preclamp - minimum\ rSO_2\ reading\ crossclamp}{mean\ rSO_2\ reading\ preclamp}$$

Figure 1: Thus, a change of rSO_2 reading from a mean preclamp value of 60% saturation to a minimal (after crossclamp) of 54% saturation according to this formula would represent a 10% decrease in rSO_2 reading (percentage change = 10%).

Serum Biomarker of Brain Injury

Venous blood samples were obtained for each patient in five-time frames: preoperatively (basal sample, preclamp), immediately after the end of the procedure (declamp), 12 hours, 24 hours, and 48 hours after the surgery. Samples were allowed to clot. Blood samples were centrifuged within 30 minutes, and serum was stored at –20°C until assayed in duplicate in a single batch within 6 months. The concentrations of NSE were measured by automated electrochemiluminescence assay (Cobas e411 analyser, Roche Diagnostics, Mannheim, Germany). The lower limit of detection for NSE was 0.04 µg/L. The upper reference limit of NSE was set at 18.3 µg/L, representing the 95th percentile of the healthy population. The reference limit was provided by the manufacturer of the assay and verified by the laboratory. We compared the baseline value with the sample taken immediately after the end of the procedure. We considered significant an increase of 25% from the reference value [12].

Statistical Analysis

The lowest values of rSO_2 and highest values of NSE were used for comparison between the group without neurological symptoms and the group having neurological symptoms. The baseline characteristics of patients who developed neurological symptoms were compared with those of patients with no symptoms using the chi-square test or Fisher exact test, where appropriate. In the case of continuous variables, the independent samples t-test or Mann-Whitney test was used. From these results, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-) and diagnostic odds ratio (DOR) with 95% confidence intervals (CI) were calculated. ROC curve analysis was applied to identify the threshold values of parameters, and the area under the curve (AUC) values were compared. Statistical analysis was performed using R 3.5.2 statistical software (R Foundation for Statistical Computing, Vienna, Austria). A p-value less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

In this study, 64 CEAs were performed under regional anaesthesia. There were 41 (67%) men and 19 (33%) women; patient mean age (±SD) was 70.9 ± 8.5 years (range, 50-86 years). Two men and two women were operated on bilaterally. Fifty-nine percent of the CEAs were performed for asymptomatic disease, compared to 41% for symptomatic disease.

Demographics, Anatomy, and Pre-Operative Variables

There were no differences (Table 1) in diabetes mellitus, hypertension, smoking, hypercholesterolaemia, coronary artery bypass graft, and chronic renal failure, or peripheral artery disease between those with and without neurological symptoms. There were no significant differences in rates of overall prior carotid intervention, symptomatic features, contralateral carotid stenosis grade, or pre-operative diagnostics between the two groups. However, ipsilateral carotid stenosis grade of 50–69% (43% vs. 12%) was more common in those with neurological symptoms, and ipsilateral carotid stenosis grade of 70–89% (57% vs. 88%) was more common in those without neurological symptoms (P = .056).

Table 1: Baseline characteristics of no neurological symptoms (NS-) and neurological symptoms (NS+) group.

Baseline characteristics	All patients (n = 64)	NS- (n = 57)	NS+ (n = 7)	p-value
Age	70.9 ± 8.5	71.0 ± 8.1	70.1 ± 12.1	0.811
Gender – male	43 (67)	39 (68)	4 (57)	0.675
Smoking – current or past	23 (36)	20 (35)	3 (43)	0.695
Hypertension	58 (91)	51 (90)	7 (100)	1
Diabetes	30 (47)	27 (47)	3 (43)	1
Hypercholesterolaemia	51 (80)	46 (81)	5 (71)	0.623
Prior PCI	10 (16)	10 (16)	–	–
Prior CABG	10 (16)	9 (16)	1 (14)	1,000
PAD	18 (28)	17 (30)	1 (14)	0.662
CRF	18(28)	16 (28)	2 (29)	1
Symptomatic features				
Symptomatic stenosis	26 (41)	22 (39)	4 (57)	0.428
TIA	12 (19)	10 (18)	2 (29)	0.607
CVI	14 (22)	12 (21)	2 (29)	0.642
Prior ipsilateral CEA/CAS				
Prior contralateral CEA	6 (9)	5 (9)	1 (14)	0.516
Prior contralateral CAS	1 (2)	1 (2)	–	–
Ipsilateral carotid stenosis grade				
50–69%	10 (16)	7 (12)	3 (43)	
70–89%	33 (51)	32 (56)	1 (14)	0.056
>90%	21 (33)	18 (32)	3 (43)	
<50%	34 (61)	32 (64)	2 (33)	
50–69%	12 (21)	9 (18)	3 (50)	0.215
>70%	10 (18)	9 (18)	1 (17)	
Contralateral carotid occlusion	8 (12)	7 (12)	1 (14)	
Pre-operative diagnostics				
Pre-operative duplex ultrasound	46 (72)	41 (72)	5 (71)	1
Pre-operative CTA	52 (81)	46 (81)	6 (86)	1

Note: Results are presented as n (%) or mean ± standard deviation. PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; PAD = peripheral arterial disease; CRF = chronic renal failure; TIA = transient ischemic attack; CVI = cerebrovascular insult; CEA = carotid endarterectomy; CAS = carotid artery stenting; CTA = computer tomographic angiography.

Operative and Post-Operative Variables

Neurological deterioration after carotid clamping occurred (neurological symptoms group) in 7 (10.9%) operations. Neurological change resolved after the insertion of an intravascular shunt. The median [1stQ, 3rdQ] duration of carotid cross-clamping was 23.2 [19.8, 28.9] minutes and 20.9 [12.4, 29.2] minutes in the no neurological and neurological symptoms groups, respectively (Table 2). This difference was not statistically significant (P = .519). A prosthetic patch was used in 58 (90.6%) procedures, and primary closure in 6 (9.4%) procedures.

Table 2: Operative in post-operative factors in patients without neurological symptoms (NS-) and patients with neurological symptoms (NS+) during CEA.

Factor	NS- (n = 57)	NS+ (n = 7)	p-value
Length of cross-clamping (min.)	23.2 [19.8–28.9]	20.9 [12.4–29.2]	0.519
rSO_2			
Base ipsilateral	69 [62–75]	62 [54–72]	0.232
Lowest ipsilateral	60 [52–67]	52 [42–65]	0.297
Post-clamp ipsilateral (% decrease)	10 [6–19]	15 [6–21]	0.675
Base contralateral	69 [63–75]	65 [48–73]	0.232
Lowest contralateral	65 [60–72]	51 [41–64]	0.042
Post-clamp contralateral (% decrease)	4 [2–8]	4 [2–15]	0.731
NSE			
Pre-clamp (µg/L)	2.94 [0.76;7.10]	3.53 [0.56;6.39]	0.667
Declamp (% increase)	-52.38 [-71.17;62.63]	30.05 [-69.52;1333]	0.25
Post op 12 h (% increase)	-53.10 [-79.85;-2.35]	46.61 [-35.69;1208]	0.026
Post op 24 h (% increase)	-42.15 [-82.16;75.27]	-12.05 [-54.96;402]	0.224
Post op 48 h (% increase)	-11.56 [-76.69;114.66]	-9.32 [-83.02;644]	0.991

Note: Results are presented as median [interquartile range]. CEA: carotid endarterectomy; rSO_2: cerebral oxygen saturation; NSE: neuron-specific enolase.

NSE

The median [1stQ, 3rdQ] baseline serum levels of NSE in the asymptomatic patients and symptomatic patients were 2.34 µg/L [0.72 µg/L, 6.11 µg/L] and 4.14 µg/L [1.08 µg/L, 7.12 µg/L], respectively. There were no significant differences in baseline preclamp concentrations of NSE between the patients (P = .473; Mann-Whitney U test). No statistically significant difference was observed in any of the categories when comparing the asymptomatic and symptomatic patients (Table 3). No statistically significant difference was observed in any of the categories when comparing the asymptomatic patients, post-CVI (post-cerebrovascular insult) patients, and post-TIA patients (Table 4). The percentage of increase in NSE parameter at different time frames for the no neurological symptoms and neurological symptoms groups is depicted in Figure 2. The median serum NSE level increase was 46.6% [-35.7%, 1208%] (median [1^{st}Q, 3^{rd}Q]) in the neurological symptoms group, compared with -53.1% [-79.9%, -2.4%] (median [1^{st}Q, 3^{rd}Q]) in the no neurological symptoms group at the time frame 12 hours after the procedure. The highest increase of serum NSE protein was 1742%. The increase was significantly different between the groups (P = .026; Mann-Whitney U test) (Table 2). This finding indicates that neurological instability that occurs after clamping correlates with the less decrease in NSE level. The threshold for NSE of 13.1 % decrease was optimal to identify patients with neurological symptoms. Applying this technique, the area under the curve (AUC) was 0.759 (95 % confidence interval CI = [0.606, 0.913]), and the diagnostic sensitivity and specificity were 71.4 % and 73.6 %, respectively (Figure 3, Table 5).

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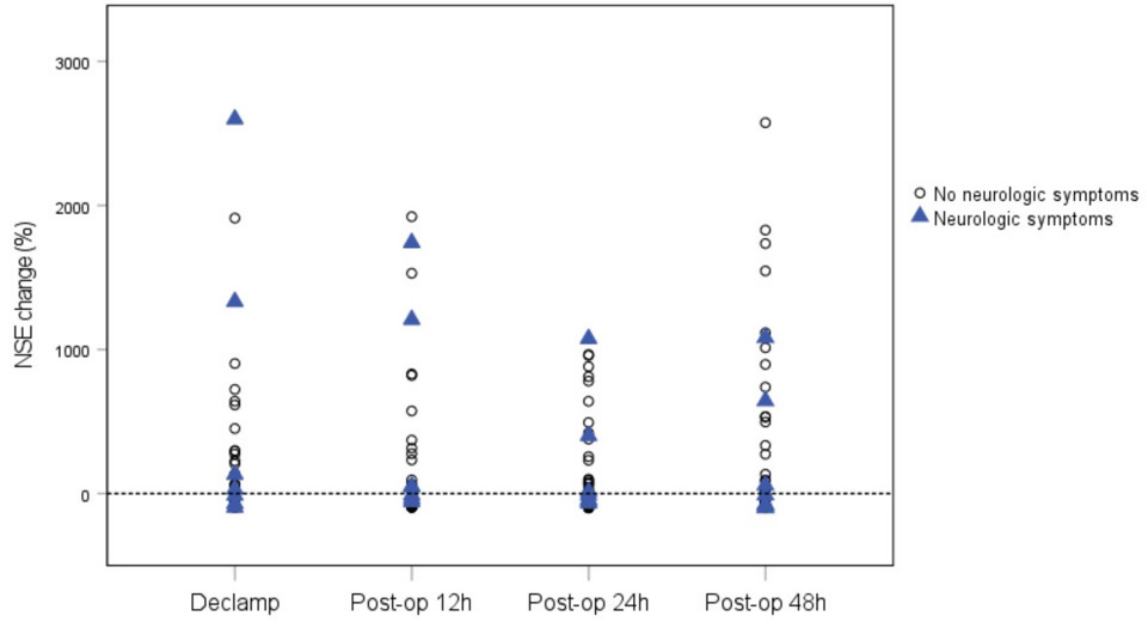

Figure 2: Percentage of increase in NSE parameter at different timeframes for the no neurological symptoms and neurological symptoms groups.

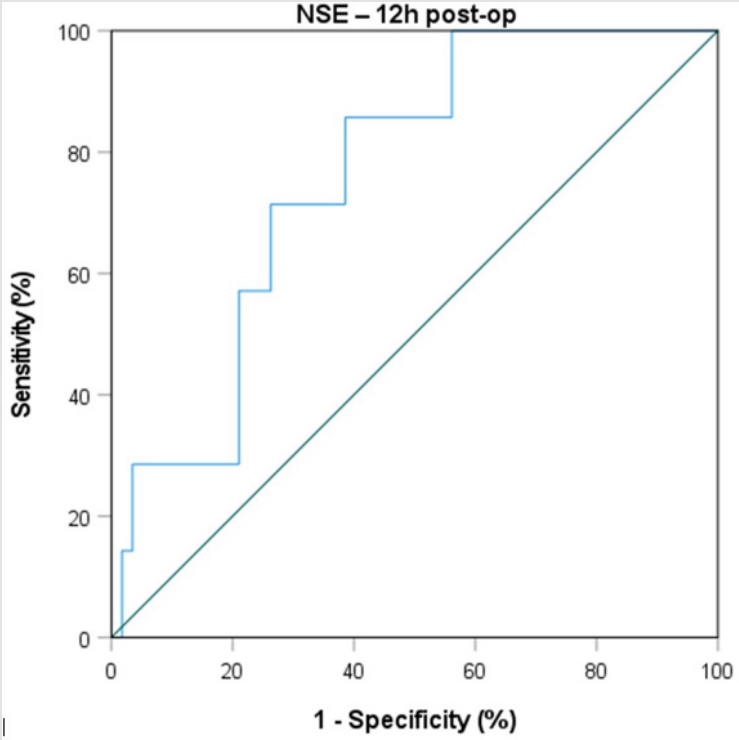

Figure 3: ROC curve for performance of NSE, 12 hours after the surgery, percentage change in prediction of neurological symptoms. The closest top left point is at threshold value -13.1 % with sensitivity of 71.4 % and specificity of 73.6 %. The area under the curve is 76 % (95 % CI: 61–91 %).

Table 3: Operative in post-operative factors in symptomatic (S) and asymptomatic (A) patients.

Factor	S (n = 26)	A (n = 38)	p-value
Length of cross-clamping (min.)	22.5 [19.2–29.6]	23.2 [20.3–28.2]	0.677
rSO_2			
Base ipsilateral	69 [64–75]	68 [61–72]	0.452
Lowest ipsilateral	61 [53–66]	58 [51–66]	0.599
Post-clamp ipsilateral (% decrease)	11 [6–23]	10 [6–17]	0.613
Base contralateral	68 [65–72]	70 [60–76]	0.538
Lowest contralateral	65 [61–68]	64 [57–73]	0.763
Post-clamp contralateral (% decrease)	3 [2–7]	5 [2–11]	0.507
NSE			
Pre-clamp (µg/L)	4.14 [1.08;7.12]	2.34 [0.72;6.11]	0.473
Declamp (% increase)	-53.02 [-66.51;76.43]	-48.88 [75.36;132.16]	0.946
Post op 12 h (% increase)	-51.23 [79.71;53.22]	-46.39 [75.51;13.48]	0.806
Post op 24 h (% increase)	-38.70 [-78.88;73.86]	-40.69 [-82.08;118.47]	0.891
Post op 48 h (% increase)	-10.98 [-75.67;99.46]	-15.76 [78.77;338.21]	0.88

Note: Results are presented as median [interquartile range]. CEA: carotid endarterectomy; rSO_2: cerebral oxygen saturation; NSE: neuron-specific enolase.

Table 4: Operative in post-operative factors in symptomatic (S-TIA or S-CVI) and asymptomatic patients (A).

Factor	S-TIA (n = 12)	S-CVI (n = 14)	A (n = 38)	p-value
Length of cross-clamping (min.)	19.3 [19.1–26.0]	25.0 [21.3–30.2]	23.2 [20.3–28.2]	0.339
rSO2				
Base ipsilateral	70 [65–76]	69 [59–72]	68 [61–72]	0.622
Lowest ipsilateral	61 [56–64]	61 [50–68]	58 [51–66]	0.855
Post-clamp ipsilateral (% decrease)	11 [7–22]	11 [6–22]	10 [6–17]	0.872
Base contralateral	70 [66–71]	67 [61–72]	70 [60–76]	0.687
Lowest contralateral	67 [63–68]	64 [54–66]	64 [57–73]	0.451
Post-clamp contralateral (% decrease)	3 [2–3]	5 [2–7]	5 [2–11]	0.423
NSE				
Pre-clamp (µg/L)	4.24 [1.26;6.19]	4.03 [0.45;7.31]	2.34 [0.72;6.11]	0.771
Declamp (% increase)	-56.33 [68.51;49.62]	-51.99 [64.56;795.2]	-48.88 [75.36;132.16]	0.813
Post op 12 h (% increase)	-45.62 [-77.94;46.93]	-51.23[-82.68;1288]	-46.39 [75.51;13.48]	0.97
Post op 24 h (% increase)	-17.28 [49.07;87.18]	-58.61 [-83.29;111.2]	-40.69 [-82.08;118.47]	0.512
Post op 48 h (% increase)	-8.81 [-50.65;80.62]	-40.18 [-80.61;384.7]	-15.76 [78.77;338.21]	0.878

Note: Results are presented as median [interquartile range]. CEA: carotid endarterectomy; rSO_2: cerebral oxygen saturation; NSE: neuron-specific enolase.

Table 5: Results of ROC curve analysis with threshold values.

	AUC (%)	Cut-off (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
rSO_2					
Post-clamp ipsilateral	55 (33;77)	13.4	57 (14;86)	63 (51;75)	63 (22;83)
Post-clamp contralateral	46 (18;74)	-2.2	14 (0;43)	98 (93;100)	89 (22;83)
NSE					
Declamp	63.4(37.9;88.4)	-16.7	71.4 (29.0;96.3)	64.9 (51.1;77.1)	65.6 (52.7;77.0)
Post-operative, 12 h	75.9(60.6;91.3)	-13.1	71.4 (29.0;96.3)	73.6 (60.3;84.5)	73.4 (60.9;83.7)
Post-operative, 24 h	64.2(46.0;82.3)	-15.2	57.1(18.4;90.1)	66.7 (52.9;78.6)	65.6 (52.7;77.0)
Post-operative, 48 h	50.0(24.9;75.4)	-9.6	57.1(18.4;90.1)	56.1 (42.3;69.3)	56.2 (43.3;68.6)

Note: Results are presented as value (95% CI). AUC: area under the curve; rSO_2: cerebral oxygen saturation.

Cerebral Oxygen Saturation

The decrease in rSO_2 from the preclamp to cross-clamp period on the ipsilateral side was not statistically significant between the groups. The median rSO_2 decrease was 15% [6%, 21%] (median [1stQ, 3rdQ]) in the neurological symptoms group and 10% [6%, 19%] (median [1stQ, 3rdQ]) in the group without neurological symptoms (P = .675, Mann-Whitney U test). The correlation between changes in rSO_2 and neurological symptoms was analysed. By ROC analysis, a cut-off of rSO_2 decrease of 13.4% was determined to be optimal for identifying patients with neurological symptoms, with an AUC of 0.5489 (95% CI = [0.3327, 0.7651]), and sensitivity and specificity of 57.1% and 63.2%, respectively (Figure 4, Table 5).

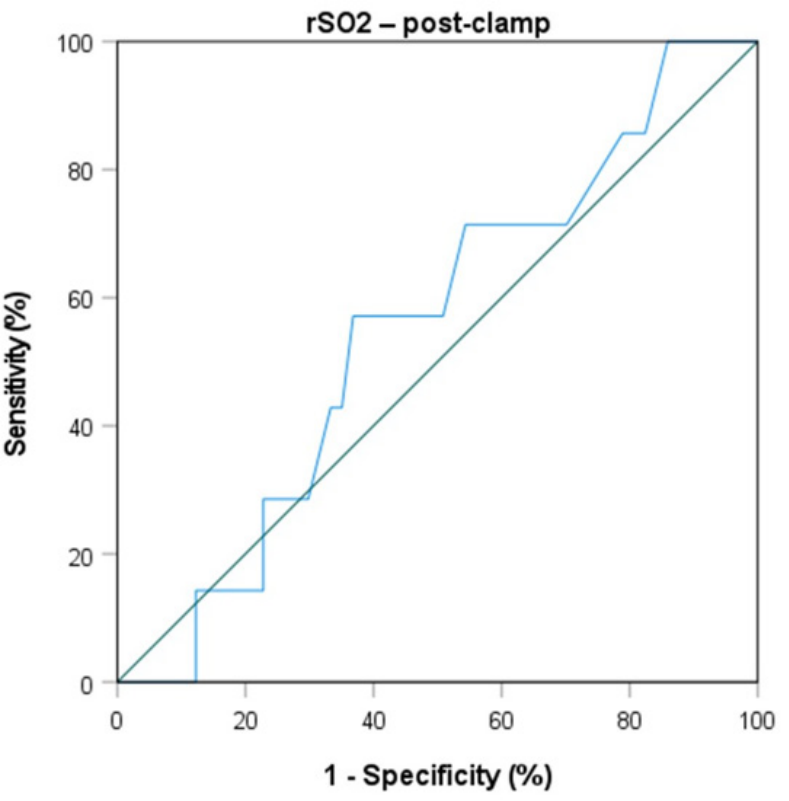

Figure 4: ROC curve for performance of rSO2 post-clamp percentage change in prediction of neurological symptoms. The area under the curve is 55 % (95 % CI: 33–77 %).

Contralateral Carotid Occlusion

There were no statistically significant differences between contralateral carotid occlusion and neurological symptoms (P = 1, Mann-Whitney U test), contralateral carotid occlusion and serum NSE increase (P = .208, Mann-Whitney U test), or contralateral carotid occlusion and rSO_2 fall (P = .418, Mann-Whitney U test).

Prediction of Neurological Symptoms

The positive predictive value (PPV) for the prediction of neurological symptoms during the CEA was 16% for the rSO_2 parameter. For the NSE parameter, the values were 20% for declamp, 25% for 12h post-operative, 17% for 24h post-operative, and 14% for 48h post-operative. The negative predictive value (NPV) for the rSO_2 parameter and NSE parameter at different timeframes were 92%, 95%, 95%, 93%, and 91%, respectively (Table 6). However, in terms of likelihood ratio (LR) considered minimally predictive, the 12h NSE parameter had the highest LR+ (2.7, 95% CI: 1.4–5.1) and lowest LR- (0.4, 95% CI: 0.1–1.3) amongst other measurements. Also, in terms of odds ratio (DOR), this parameter performed best (7.0, 95% CI: 1.2–39.9).

Table 6: Performance of rSO_2 and NSE parameters in prediction of neurological symptoms.

	PPV (%)	NPV (%)	LR+	LR-	DOR
rSO_2 NSE	16 (8;28)	92 (83;97)	1.6 (0.8;3.2)	0.7 (0.3;1.6)	2.3 (0.5;11.2)
Declamp	20 (12;31)	95 (85;98)	2.0 (1.1;3.6)	0.4 (0.1;1.4)	4.6 (8.2;26.0)
Post-operative, 12 h	25 (7;53)	95 (86;98)	2.7 (1.4;5.1)	0.4 (0.1;1.3)	7.0 (1.2;39.9)
Post-operative, 24 h	17 (15;39)	93 (85;96)	1.7 (0.8;3.6)	0.6 (0.3;1.5)	2.7 (0.5;13.1)
Post-operative, 48 h	14 (7;24)	91 (81;96)	1.3 (0.6;2.6)	0.8 (0.3;1.8)	1.7 (0.3;8.3)

Note: Results are presented as value (95% CI). DOR: odds ratio; LR-: negative likelihood ratio; LR+: positive likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; NSE: neuron-specific enolase; rSO_2: cerebral oxygen saturation;

Perioperative Outcomes

Two (3.1%) perioperative strokes occurred. The single major stroke happened on day 6, and the patient had decreased responsiveness to verbal commands and developed left hemiplegia. The diagnosis of stroke was based on the clinical and computed tomography findings of a focal ipsilateral ischaemic cerebral infarct with a patent CEA site on angiography. The patient was asymptomatic. The other patient had mild neurological deficits with complete recovery without re-exploration of the carotid artery. The patient was symptomatic. Both patients were shunted and had normal rSO_2. The relative increase in NSE occurred in the first of the two patients. In the second patient, NSE did not increase.

Discussion

The current study aims to evaluate the role of NSE as a biomarker in tracking the progression brain parenchymal injury before the onset of clinical symptoms. NSE is a cytoplazmic protein found in neuronal cells, and its release into the bloodstream at significantly high levels indicates neuronal damage, according to (Bharosay, et al. [22]). They reported that endothelial cell death disrupts the blood-brain barrier during a stroke, and the released cytoplasmic contents from damaged brain tissues disseminate through it. Thus, it is crucial to have highly sensitive brain markers that can be detected in blood rather than cerebrospinal fluid [23]. NSE is recognized as a neuronal marker in the human brain and is only found in trace quantities in the blood. Earlier studies [24] have demonstrated that injured neurons release NSE in the first hours, indicating functional abnormalities or plasma membrane structural disorder due to brain ischaemia. Although biomarkers are associated with cerebral ischaemia, their successful translation into a useful clinical differential diagnostic tool has been challenging [11] [25]. Seven studies have reported increased NSE levels ranging from 4 to 8 hours post-ischaemia [26]. The mechanism behind serum NSE elevation observed in our study is unknown. However, we support the hypothesis that increased blood-brain barrier permeability caused by hypoxia during carotid cross-clamping may contribute to NSE leakage from the brain into the blood [27].

Cerebral damage during carotid clamping may result from microembolism and/or hypoperfusion. Elevated serum NSE levels may reflect ischemia-induced enzyme loss. An increase in serum NSE level may also be caused by hyperperfusion brain damage during CEA. In many patients, clamping of the ICA during CEA results in transient decrease in cerebral blood flow in the ipsilateral cerebral hemisphere [28]. If this decrease in the hemispheric cerebral blood flow is significant enough to impair autoregulation, then consequently ipsilateral cerebral hyperperfusion can occur after ICA declamping. The development of cerebral hyperperfusion after CEA is associated with preoperative hemodynamic impairment and intraoperative cerebral ischemia [29]. It has been suggested that acute ischemia and reperfusion by clamping and declamping of the ICA may produce oxygen-derived free radicals resulting in impairment of cerebrovascular autoregulation, postischemic hyperperfusion, or brain oedema [30,31]. The main finding of this pilot study was that the serum NSE protein level, as a marker of cerebral injury, correlates significantly with neurological instability at the 12-hour timeframe after CEA. This correlation was not observed in the measurements based on the other three timeframes: declamp, 24 hours, and 48 hours. The difficulty with the results was that we detected a decrease in NSE levels in all four measurement phases, but the drop was the smallest at 12 hours.

Based on previous studies, an increase in NSE levels was expected during the surgical procedure, not a decrease. The deviation observed at the 12-hour timeframe was statistically significantly different between the groups without neurological symptomatic and with neurological symptoms. However, in our case, it was a decrease in serum NSE concentration. We do not yet have an explanation for this phenomenon. As we mainly monitor changes in values compared to the previous state, which could be caused by surgical manipulation, hypothetically these values could also help us determine ischaemic conditions. An increase in NSE appears relatively late, after the surgical procedure has already ended. Due to its late appearance, it could not be used as an indicator to detect ischaemia during the surgical procedure. An additional challenge that arises is the extent of brain damage. In CEA surgery, the brain damage is relatively small and usually not clinically detectable. (Fassbender, et al. [32] and colleagues reported that serum NSE levels are less sensitive when the damage to the brain is small, barely exceeding the reference value, and a larger degree of damage is needed to yield a reliably detectable difference.

Such findings are consistent with a study conducted by (Brea, et al. [33]) and colleagues, who reported that the peak serum NSE concentration associated with stroke severity was assessed at admission using the National Institutes of Health Stroke Scale (NIHSS). (Jauch, et al. [34]) and colleagues also reported that higher 24-hour maximum NSE concentrations were associated with higher baseline NIHSS scores.

Seven (10.9%) patients who required shunting developed cerebral ischaemia (neurological deficit) during carotid clamping. These results are similar to those reported by Hans (10%) [35], Evans (9.7%) [36], Calligaro (7.2%) [37], Stroughton, et al. (14%) [38], and Rockman, et al. (11%) [39] for CEA in awake patients. In particular, of the 7 patients who required shunting due to the lack of compensatory blood flow, four patients were in the NSE-positive group. We did not find that neurological change could be predicted as a function of NSE marker increase, as NSE decreased in all time points, but the decrease was less at the timeframe of 12 hours. A less decrease could predict neurological change with a sensitivity and specificity of 71.4% and 73.6%, respectively. The cut-off value for neurological symptoms was a decrease of 13.1%. Different results were obtained in studies conducted by Rasmussen [40]. The authors measured serum levels of NSE in patients before CEA and postoperatively at 12, 24, 36, and 48 hours. Compared with abdominal aortic surgery patients, the preoperative serum level of NSE was significantly higher in carotid artery surgery patients. Postoperatively, serum NSE level decreased significantly after uncomplicated CEA, and the level was then similar to that in the aortic surgery patients. The authors [27] concluded that subtle brain damage after carotid artery surgery could not be detected by measuring blood levels of NSE. There are different release patterns of NSE during CEA in LA.

The variations of NSE concentrations seemed to be influenced by cerebral perfusion alterations during carotid clamping and the use of a shunt, even in the presence of adequate collateral brain circulation. The routine use of shunting in symptomatic patients appears to have the potential to prevent the increase of serum NSE concentrations after carotid endarterectomy in LA [15]. In addition, GA may have various effects on cognition. Previous studies have suggested that LA may be preferable to GA with regard to the effects on cognitive function [41,42]. We found higher preclamp concentrations in symptomatic patients than in asymptomatic patients. The difference was not statistically significant (P = .473, Mann-Whitney U test). The same was found by (Dragas, et al. [15]). But he found significantly higher preclamp S100B concentrations in symptomatic patients. This was explained by the greater embolic potential of symptomatic carotid plaques [13]. (Falkensammer, et al. [13]) found the highest concentration of NSE 4 hours after the procedure, with a fall 24 hours after the procedure. The decrease in rSO_2 from the preclamp to cross-clamp period on the ipsilateral side was not significantly greater in the neurologic symptoms group (P = .675). Moreover, the low AUC value suggests that the correlation between the percentage drop in rSO_2 and neurological symptoms is a weak one at best. The relative drop in rSO_2 is neither sensitive (57.1%) nor specific (63.2%) in detecting patients with neurological symptoms.

These data do not support the use of cerebral oximetry as the sole monitoring modality during CEA. The absolute lowest value of rSO_2 on the contralateral side was statistically different (P = .042) between the groups. However, this difference has no clinical implications since there is considerable inter-individual variation in baseline measures of rSO_2 [43,44], with a wide range of baseline rSO_2 values, varying from 47% to 86%. Therefore, it is appropriate to use relative changes in rSO_2 rather than absolute values [45]. Previous studies using rSO_2 have shown better preservation of cerebral oxygenation levels, cytochrome oxidase levels, and perfusion during surgery under LA compared with GA [46]. These potential benefits were associated with a significant rise in systemic blood pressure in LA patients following carotid clamping [17]. One limitation of the currently available rSO_2 monitoring technology is that the oxygen sensor can only be applied to the hair-free areas of the scalp. Therefore, focal cerebral ischaemia in other parts of the brain may develop without a decrease in rSO_2 registered by the sensors placed on the forehead [19]. It is not yet known how much of a critical fall in rSO_2 the brain can tolerate [1]. In our study, we determined that a 13% (13.4%) decrease in rSO_2 as optimal for detecting patients with neurological symptoms, with a sensitivity and specificity of 57.1% and 63.2%, respectively. This result is similar to those of al-Rawi [20] and Mille [21], with cut-off values of 13% and 12% (11.7%), respectively.

There were 8 patients with the presence of a contralateral carotid occlusion. One of them fell into the neurological symptoms group, two had an increased serum level of NSE, and two had a significant fall in rSO_2. Contralateral carotid occlusion cannot reliably predict the need for a shunt. Two patients suffered cerebrovascular insult (CVI). The patient who suffered a CVI during the procedure had an increased serum NSE level, but her rSO_2 was normal. More extensive cerebral injuries are associated with higher serum NSE levels with relatively late peak times. Patients with subclinical cerebral tissue death exhibit lower and progressively earlier peak serum levels [27]. The other patient suffered a CVI on day 6 after the procedure. The increase in serum NSE was not significant, and the rSO_2 remained normal. The neurological instability predicted the CVI attack, which was not true for increased levels of NSE and rSO_2. Awake neuromonitoring is inherently specific for CEA under LA and has been shown to be a sensitive direct measure of cerebral tissue perfusion. We found a correlation between neurological symptoms and an increase in NSE. Monitoring of serum NSE during the CEA cannot be performed because of the long evaluation time (usually requiring ≥3 hours to perform). Due to the small number of patients in our study, especially those assigned to the neurological symptoms group, we cannot draw firm conclusions. Future studies will either confirm our results or refute them.

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