Clinical Study

Somatosensory evoked potentials in carotid artery stenting: Effectiveness in ascertaining cerebral ischemic events

Somatosensory evoked potentials (SSEP) have been used in various endovascular procedures and carotid endarterectomy but to our knowledge no literature deals exclusively with its utility in carotid artery stenting (CAS). The purpose of this study was to evaluate the efficacy of SSEP in detecting cerebral ischemic events during CAS. We conducted a prospective study in 35 CAS procedures in 31 patients during an 18 month period. Thirty-three patients without near occlusion underwent stenting using dual protection (simultaneous flow reversal and distal filter) combined with blood aspiration, while two patients with near occlusion underwent stenting without dual protection. All 35 patients underwent SSEP monitoring. SSEP were generated by stimulating median and/or tibial nerves and recorded by scalp electrodes. During the aspiration phase post-dilation, seven patients (20%) exhibited SSEP changes with a mean duration of 11.3 ± 8.5 minutes (range: 3–25 minutes), three of whom later developed minor stroke/transient ischemic attack. Diffusion-weighted imaging showed new lesions in 10 patients (28.6%). Change in SSEP exhibited mean sensitivity of 100% (95% confidence interval, 0.29–1.0) and specificity of 88% (95% confidence interval, 0.71–0.96) in predicting clinical stroke post-CAS. Intra-procedural SSEP change was predictive of post-procedural complications (p = 0.005, Fisher’s exact test). Longer span of SSEP change was positively correlated with complications (p = 0.032, Mann–Whitney test). Intra-procedural SSEP changes are highly sensitive in predicting neurological outcome following CAS. Chances of complications are increased with prolongation of such changes. SSEP allows for prompt intra-procedural ischemia prevention measures and stratification to pursue an aggressive peri-procedural protocol for high risk patients to mitigate neurological deficits.

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1. Introduction

Somatosensory evoked potentials (SSEP) have been used in different neurosurgical procedures for decades with varying degrees of success in ascertaining ischemic events, usually in conjunction with electroencephalogram (EEG), cerebral oximetry and stump pressure measurements [1–8]. The standard SSEP technique utilizes the dorsal column-lemniscal system to non-invasively assess the functional integrity of the somatosensory cortex [4,9]. Monitoring SSEP in the median nerve (MN) and/or tibial nerve (TN) is a technically simple and proven method in determining ischemic events in middle cerebral artery territory [1,4,6,9].

Carotid artery stenting (CAS) is a less invasive revascularization alternative to carotid endarterectomy (CEA). Risk of stroke due to intra-procedural hemodynamic disturbances or debris migration from internal carotid artery plaques causing distal embolism is the main complication of CAS [10,11]. Peri-procedural minor ischemic stroke incidence following CAS is twice than that of CEA [12]. Rates of new diffusion-weighted imaging (DWI) lesions following CAS are as high as 50%, three times that of CEA [13]. Occurrence of these minor strokes despite rapid advances in technology and technique suggests that there is room for improvement in terms of intra-procedural neuroprotection.

The benefits of SSEP in CEA [1,6,8] and various endovascular techniques [2–4,7] have been well established. However, the authors are unaware of any literature in the English language that has exclusively reported on SSEP monitoring in CAS. The aim of this study was to evaluate the efficacy of SSEP in detecting cerebral ischemic events during CAS.
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2. Materials and methods

2.1. Patients

The Institutional Review Board approved the study protocol. All patients undergoing CAS from October 2013 to March 2015 at Hiroshima University Hospital, Japan were included in this prospective study. Written consent was obtained from all participants. After excluding cases with inadequate/unreadable recordings due to decrease in signal/noise ratio, 35 CAS procedures in 31 patients (28 men, mean age 72.6 ± standard deviation [SD] of 6.3 years, range: 58–83) were included in the final study. Five patients underwent bilateral CAS, four of them in the same setting and one after a 5 week interval. One patient undergoing bilateral CAS on the same day refused SSEP on the second side. All except two cases of near occlusion underwent CAS using dual protection (simultaneous flow reversal and distal filter) combined with blood aspiration [14].

2.2. Time-of-flight MR angiography and DWI

MRI was performed on a 3 Tesla MRI unit (Signa Excite HD 3.0T; General Electric, Milwaukee, WI, USA) using an eight channel NeuroVascular phased array coil. Maximum intensity projection images from time-of-flight MR angiography were obtained using the following parameters: repetition time 20 ms; echo time 3.4 ms; flip angle 18°; field of view 240 × 240 mm; matrix 256 × 160 (recon 512 × 512); and slice thickness 2.4 mm. Both pre- and post-procedural DWI (b = 1,000 s/mm²) were obtained using spin echo planar imaging sequences oriented in the axial plane; effective gradient 40 mT/m; slew rate 150 mT/m/ms. The parameters were: repetition time 5000 ms; echo time 73.2 ms; NEX 1; field of view 220 × 220 mm; slice thickness 6 mm; intersection gap 1.0 mm; number of slices 20; data acquisition matrix 128 × 128 mm; one acquisition.

2.3. Post-procedural evaluation

Stroke was defined as new neurological deficits lasting >24 hours. Stroke that resolved completely within 30 days and ≥30 days of follow-up were defined as minor and major stroke, respectively. Occurrence of major stroke, myocardial infarction, or death after CAS were defined as major adverse events. DWI acquired within 3 days before and after CAS were compared to evaluate CAS-related hyperintensities.

2.4. SSEP method

All procedures were performed under local anesthesia. SSEP were generated by stimulation using surface electrodes over MN at the wrist (± TN at ankle). For cortical recordings, the international 10/20 EEG system was followed. Scalp electrodes were placed at C3, C4, Cz, and Fpz. Pulse intensity was set above the motoric pulse threshold, but at tolerable level of abductor pollicis brevis (10–20 mA) for MN, and flexor hallucis longus (15–25 mA) for TN, recognized by visible contractions. Stimulation parameters consisted of constant voltage, 0.3 ms duration for MN and 0.5 ms for TN, with bandpass filter of 10–250 Hz. A minimum of 250 sweeps at 3.3 Hz was averaged. Recordings were done using Nicolet Viking Electrodiagnostic System (Nicolet Instruments, Madison, WI, USA).

In different settings, either unilateral or bilateral alternating side to side stimulation of MN was carried out. Bilateral MN stimulation was done in five patients, MN and TN in six, TN only in one and MN only in 23 patients. Three to four “initial control” waves were recorded at different intervals prior to inflation of occlusion balloons. All subsequent SSEP were compared with these and scrutinized. SSEP were continuously recorded during stenting.

The following definitions were used to quantify SSEP changes. A significant SSEP change was an amplitude reduction of >50% and/or latency delay (N20/P24 or P40/N48) of >10%. Changes were classified as permanent if they persisted until the end of the procedure. Any persistent deviation in the obligate waveform morphology from the initial controls was deemed urgent enough to warrant a verbal warning to the operating surgeons.

CAS protocol, procedure and post-procedural management at the study center has been previously published by Sakamoto et al. [10,14].

Statistical analysis was done using Stata 13 (StataCorp., College Station, TX, USA). Odds ratios and 95% confidence intervals (CI) were calculated using logistic regression analysis. Categorical variables were analyzed using Fisher’s exact test. The Mann–Whitney test was used for quantitative variables. Unpaired t-test was used to compare means of independent groups. A p value of ≤0.05 was considered statistically significant.

3. Results

Of the 35 CAS performed on 31 patients (mean age 72.6 ± SD 6.3 years, range: 58–83 years), seven patients (20%) exhibited significant SSEP changes. Obsolete SSEP waveform morphology was aberrant and slightly earlier than clinical manifestations in four patients. In three patients, there were no corresponding clinical signs of brain ischemia. In all seven patients, SSEP changes (mean duration 11.3 ± SD 8.5 minutes, range: 3–25 minutes) started during the aspiration phase post-dilation, and operating surgeons were notified accordingly. None of the SSEP changes were permanent.

3.1. Post-procedural evaluation

DWI showed newly developed small hyperintense spots in 10 (28.6%) patients.

The overall technical success rate of CAS was 100%. The mean procedure time from femoral artery puncture to sheath removal was 82.4 ± SD 15.2 minutes. There was no incidence of a major adverse event post-procedure. Minor stroke occurred in two patients: dysarthria for 6 days and motor aphasia and hemiparesis for 7 days. Transient ischemic attack occurred in one patient, who experienced unilateral spatial neglect for 2 hours and dysarthria for 6 hours post-CAS that resolved in the next 2 hours. In patients with SSEP changes, incidence of neurological deficit was 3/7 (42.9%). None of the cases without SSEP changes exhibited any neurological deficit (Table 1–3).

From the above findings, the sensitivity and specificity of SSEP in predicting clinical stroke post-procedure were 100% (95% CI, 0.29–1.0) and 88% (95% CI, 0.71–0.96), respectively. The positive predictive value of SSEP changes for post-procedural complications was 43% (95% CI, 0.1–0.82), while the negative predictive value was 100% (95% CI, 0.88–1.0). The diagnostic odds ratio and relative risk for patients with complications with changes in SSEP were 44.3 (95% CI, 1.95–1009.6) and 25.4 (95% CI, 1.46–442.2), respectively.

An unpaired t-test for stump pressure just prior to stenting between the group with SSEP changes (mean 39.14 ± SD 6.62 mmHg) and the group without SSEP changes (mean 49.27 ± SD 18.39 mmHg) was not statistically significant (p = 0.17).

Factors including sex, age, and laterality of the procedure were not predictors of complications. New DWI lesions were strongly

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Our study indicated that SSEP changes during CAS has strong positive correlation with post-procedural ischemic complications. Complications were also positively correlated with prolongation of SSEP changes.

SSEP in endovascular setting serves the main purpose of detecting impending ischemia. Somatosensory cortical projections of MN and TN situated on hemispheric convexity in the carotid artery territory are readily accessible to scalp electrodes. Effects of anesthesia on SSEP were irrelevant as all cases were performed under local anesthesia. SSEP are less subjective to interpretation than EEG. SSEP requires fewer scalp electrodes than EEG which could otherwise obscure real-time unsubtracted angiographic projections. At no point during this study did SSEP impede the stenting procedure, lengthening the surgical time. SSEP averaged at 250 sweeps completed in 85–90 seconds, except when the rejection rate was high due to excessive noise. However, aberration in waveform morphology is evident quite early during real time analysis. This important observation provides a crucial time window to relay warning of danger signs to the operating surgeons. Risk of major stroke after CAS is <1% [12]. Though mid- to long-term risk of stroke is similar in CAS and CEA patients, ipsilateral and ischemic peri-procedural stroke risk is higher in CAS patients [12,15,16].

A symptomatic 78-year-old man with North American Symptomatic Carotid Endarterectomy Trial (NASCET) 50% stenosis in his left carotid underwent CAS by dual protection and blood aspiration method. A self-expanding 8 mm PRECISE PRO Rx stent (Cordis Johnson & Johnson, NV, USA) was deployed. Post-dilation was performed with a 6 mm Jackal Rx angioplasty catheter (Kaneka, Osaka, Japan) (Fig. 1). SSEP changes started at the beginning of the aspiration phase (Fig. 2). Mean arterial pressure decreased from 160 mmHg to 100 mmHg and the patient exhibited motor aphasia, hemiparesis and restlessness. Etilerine hydrochloride 1 mg was injected to increase mean arterial pressure. The severity of symptoms lessened in 20 minutes. Changes in SSEP persisted for 25 minutes. There was no residual stenosis or protruding plaque after CAS. Debris was caught in the strainer and distal filter. DWI showed new hyperintense lesions (Fig. 3). His symptoms resolved completely in a week.

5. Discussion

Our study indicated that SSEP changes during CAS has strong sensitivity of 100% and slightly lower specificity of 88% in detecting post-procedural ischemic complications. Complications were also positively correlated with prolongation of SSEP changes.

SSEP in endovascular setting serves the main purpose of detecting impending ischemia. Somatosensory cortical projections of MN and TN situated on hemispheric convexity in the carotid artery territory are readily accessible to scalp electrodes. Effects of anesthesia on SSEP were irrelevant as all cases were performed under local anesthesia. SSEP are less subjective to interpretation than EEG. SSEP requires fewer scalp electrodes than EEG which could otherwise obscure real-time unsubtracted angiographic projections. At no point during this study did SSEP impede the stenting procedure, lengthening the surgical time. SSEP averaged at 250 sweeps completed in 85–90 seconds, except when the rejection rate was high due to excessive noise. However, aberration in waveform morphology is evident quite early during real time analysis. This important observation provides a crucial time window to relay warning of danger signs to the operating surgeons. Risk of major stroke after CAS is <1% [12]. Though mid- to long-term risk of stroke is similar in CAS and CEA patients, ipsilateral and ischemic peri-procedural stroke risk is higher in CAS patients [12,15,16]. Older patients and left sided procedure are also risk factors for stroke following CAS [17]. Minor strokes usually occur early, typically on the same day of the procedure [12], and are mostly caused by hemodynamic mechanisms [15]. In contrast, major strokes including hemorrhagic stroke tend to occur several days after CEA, and are most often caused by hyperperfusion [15]. Hemodynamic depression results from manipulation of the carotid sinus and baroreceptor dysfunction, prolonged clamping or difficulty in shunting during CEA, and balloon dilation [15] and aspiration during CAS. Huibers et al. report that 97% of strokes after CAS are ischemic, whereas 18% of strokes following CEA are hemorrhagic [15]. Cerebral deficits due to carotid embolization are mostly intra-procedural when debris is released spontaneously or manipulation of the plaque is technically challenging [15]. Hemorrhagic strokes on the other hand are preceded by hypertension [15].

Transient ischemic attack caused due to micro-emboi [10,11,18] is an independent predictor of decreased survival at 5 year follow up [19]. Use of an embolic protection device, as done at our center [10,14], has been positively correlated with decrease in occurrence of stroke or death at 30 day follow up [18]. However, DWI positivity still occurs frequently with embolic protection device use. Embolic debris is caught by a strainer (in the aspiration...
and/or a distal filter, and capture can only be confirmed after the filter is withdrawn at the end of the procedure. We correlated SSEP changes with new DWI hyperintensities and subsequent complications, which is a composite consequence of both hemodynamic and embolic phenomena, as opposed to debris (or intra-procedural symptoms) that takes only intra-procedural embolic phenomenon into account. In our study 10 patients (28.6%) were DWI positive which compares favorably to the 50.4% reported by the ICSS-MRI substudy [13].

In this series, seven patients (20%) exhibited significant SSEP changes. Phillips et al. report that rate of SSEP changes in intracranial aneurysm surgery range from 7–30% (average 18%) while it is
A meta-analysis of 15 studies on SSEP use in CEA reported significant SSEP changes in 11.3%, and perioperative stroke is almost guaranteed (97%) in patients with irreversible SSEP [6]. We evaluated the correlation between SSEP changes and ischemic complications post-procedure. The positive predictive value of SSEP changes leading to post-procedural complication was 43% (95% CI, 0.1–0.82). A negative predictive value of 100% (95% CI, 0.88–1.0) indicates that none of the patients without SSEP changes during CAS experienced post-procedural complications.

Pure grey matter ischemia causes distortion of obligatory waveform peaks without latency changes, whereas in white matter ischemia, latency increases initially followed by waveform distortion as conduction block ensues [9]. Symon et al. reported that at 14–16 ml/100 g/minute regional cerebral blood flow a sharp decline in evoked responses occurs, with a 50% reduction at 16 ml/100 g/minute [20]. This flow threshold for failure of neuronal electrical function [20] corresponds to prolongation of central conduction time >10 ms and is indicative of ischemia and impending infarction [7]. Ion pump failure occurs at 10–12 ml/100 g/minute [6]. Reversing the hemodynamics during this narrow window determines the viability of the perfused tissue.

Reporting on SSEP changes in neuroendovascular procedures, Phillips et al. concluded that decreased duration and reversal of changes are associated with lower incidence of postoperative infarction [4]. A meta-analysis of SSEP in CEA reported that the odds of observing SSEP changes in patients with neurologic deficits were 14 times higher than those without deficits [6]. It was 44 times higher in this series. However, no cut-off time limit for evoked potential changes for impending infarction has been established [7]. In this study, though all SSEP changes reverted to initial control levels, patients with longer duration of SSEP changes exhibited post-procedural complications and this was statistically significant.

This study has several limitations. It was a single center, non-randomized study. Small sample size coupled with limited number of events restricted the analysis to a univariate model. This limits the study in confidently determining the roles of multiple confounding factors. True sensitivity or specificity can be calculated...
only in cases where SSEP changes warning did not give rise to any interactive strategy, which is not ethical and contradicts the essence of this study.

6. Conclusion

Intra-procedural SSEP changes are highly sensitive in predicting neurological outcome following CAS. Chances of complications are increased with prolongation of such changes. SSEP is technically easier to perform in an endovascular setting and allows for prompt intra-procedural ischemic preventative measures and stratification to pursue an aggressive peri-procedural protocol for high risk patients to mitigate neurological deficits.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References


