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Assessment of cerebral blood flow changes in nonconvulsive status epilepticus in comatose patients: A pathophysiological transcranial Doppler study☆

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ABSTRACT

Purpose: We assessed the accuracy of transcranial Doppler (TCD) in helping to diagnose nonconvulsive status epilepticus (NCSE) in comatose patients admitted to the intensive care unit (ICU) for acute neurological disorders at high risk for NCSE.
Methods: A 2-year prospective observational study in 38 consecutive patients requiring continuous electroencephalography (EEG) monitoring and intracranial pressure monitoring with TCD.
Results: Of the 38 patients, 10 (26.3%) had NCSE by continuous EEG monitoring. Bilateral mean and maximal systolic and diastolic TCD velocities were significantly different between patients with and those without NCSE. Areas under the receiver-operating characteristic (ROC) curves of mean and maximal systolic velocities by TCD were 0.82 (95%CI, 0.64–1.00) and 0.79 (95%CI, 0.62–0.95) with cutoffs of 95 cm/s and 105 cm/s, respectively. Areas under the ROC curves of mean and maximal diastolic velocities were 0.76 (95%CI, 0.56–0.95) and 0.78 (95%CI, 0.60–0.96) with cutoffs of 31 cm/s and 40 cm/s, respectively. For none of the velocity parameters did the areas under the ROC curves differ significantly between the left and right sides. The best performance was obtained using mean systolic (SV) and a cutoff of 95 cm/s, which yielded a positive likelihood ratio of 3.8 and a negative likelihood ratio of 0.25.
Conclusion: Our preliminary results showed a significant association between increased TCD velocities and NCSE in comatose patients. However, the likelihood ratios suggested a limited role for TCD in helping to diagnose seizure activity. Further studies with larger samples of NCSE patients are warranted to determine the exact contribution of TCD for NCSE detection in comatose ICU patients.

1. Introduction

Nonconvulsive status epilepticus (NCSE) is a heterogeneous and complex electro-clinical condition manifesting as behavioral and mental alterations combined with continuous epileptiform discharges.[1] In a study of comatose patients who had no clinical seizures, electroencephalography (EEG) showed NCSE in 8% of cases.[2] Up to 20% of patients with convulsive status epilepticus have persistent NCSE after treatment [3] and 44% of patients in post-anoxic coma have NCSE [4]. NCSE is a severe complication associated with high morbidity and mortality rates and must therefore be diagnosed promptly.[3,5–7]

EEG monitoring is the reference standard for diagnosing NCSE. However, EEG changes related to NCSE may be difficult to differentiate from those produced by other causes of coma, such as encephalopathy.[1] Therefore, additional investigations may be useful in comatose patients with suspected NCSE. The bispectral index has been used to diagnose seizures in a few patients but has not been evaluated in prospective studies.[8] Transcranial Doppler ultrasound (TCD) is a noninvasive investigation that can be easily performed in the intensive care unit (ICU) and that reliably detects cerebral blood flow (CBF) alterations by measuring blood velocities in the basal cerebral arteries, including the middle cerebral artery (MCA).[9]

As NCSE is associated with an increase in CBF,[10] we hypothesized that NCSE was associated with CBF changes that were detectable by TCD.[11–14] We assessed this hypothesis in a

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prospective observational study of the diagnostic accuracy of TCD for NCSE detection in comatose ICU patients. The reference standard was continuous EEG monitoring. We also measured optic nerve sheath diameter (ONSD) using ocular ultrasonography to detect increases in intracranial pressure. ONSD has been validated as a good surrogate for invasive intracran ial pressure measurement.[15–17]

2. Materials and methods

The ethics committee of the French Society for Critical Care approved this prospective observational study and waived the need for written informed consent.

2.1. Patients

Consecutive comatose adults admitted to our ICU between November 2009 and November 2011 were included prospectively if they required EEG and intracranial pressure monitoring. Patients with ocular trauma or a known history of ocular disease (e.g., glaucoma or cataract) were not included. We did not include patients in whom EEG, TCD, and ONSD could not be performed simultaneously.

2.2. Definitions

Coma was defined as a Glasgow Coma Scale (GCS) score lower than 9.[18] NCSE in comatose patients with or without subtle convulsive movements (rhythmic twitching of the arms, legs, trunk, or facial muscles; tonic eye deviation; or nystagmoid eye jerking)[19] was defined as EEG findings of continuous or recurrent epilepsy-like activity including rhythmic focal or generalized spikes, sharp waves, or rhythmic waves changing in amplitude, frequency, and/or spatial distribution[20] and lasting more than 5 min.

2.3. Investigations for causes of coma

After a careful history and thorough physical examinations on scene and at ICU admission, including neurological evaluations, investigations were performed as appropriate to identify the factors causing the coma. Laboratory tests were obtained routinely. Plasma anticonvulsant drug assays and qualitative tests for toxic substances or medications associated with coma were performed at the discretion of the attending physicians. Cerebral imaging and EEG monitoring were obtained routinely. Lumbar puncture was performed when there was a fever or clinical suspicion of meningitis and when deemed appropriate by the attending physicians. The primary cause of coma was classified as cardiac arrest, subtle status epilepticus, stroke, hypoglycemia, bacterial meningitis, hypoxemia, or traumatic brain injury.

2.4. Investigations for nonconvulsive status epilepticus

The reference standard for diagnosing NCSE was bipolar 8-channel continuous EEG monitoring (Neurosoft Neuron Spectrum 4, Neurosoft, Ivanovo, Russia), via scalp electrodes positioned according to the Standard International 10–20 system (Fp2-T4, T4-O2, Fp2-C4, C4-O2, Fp1-T3, T3-O1, Fp1-C3, and C3-O2). EEG monitoring was performed and interpreted by a qualified neurophysiologist (SL).

TCD (EnVisor CHD ultrasound machine, Philips, Amsterdam, The Netherlands) was performed routinely as previously described[9] by a single trained investigator (SM) in the minutes after EEG monitoring initiation.[17,21] TCD was first performed on the right and left MCAs through the temporal window as described by Aaslid et al.[9] Systolic (SV), end-diastolic (DV), and mean (MV) velocities were recorded. The pulsatility index (PI) was calculated as [PI = (SV − DV)/MV]. Maximal MCA PI was the left or right MCA PI value, whichever was higher, and mean MCA PI the mean of the left and right MCA PI values. Mean and maximal SVs and mean and maximal DVs were obtained in the same way.

Immediately after TCD measurements, the same investigator (SM) used the same ultrasound machine to measure ONSD 3 mm behind the ocular globe, inside the dura mater in the transverse and sagittal planes[15–17]; the mean value of these two measurements was defined as the ONSD for each eye.[16] Maximal ONSD was the left or right ONSD value, whichever was higher.

2.5. Management of comatose patients in the ICU

All patients received mechanical ventilation. Measures were taken to stabilize hemodynamics as needed. Hypoglycemia was looked for routinely and corrected if present. If glucose was given, 100 mg of thiamine was administered concomitantly, most notably when there was evidence of vitamin B1 deficiency. Patients were routinely evaluated for hyperthermia, hyperglycemia, hypo- or hypercarbia, anemia, metabolic disturbances, epileptic activity, and aspiration pneumonia; all such disorders were corrected promptly. When EEG monitoring showed NCSE, anesthetic drugs (propofol and/or midazolam and/or thiopental) were given in titrated doses to induce EEG burst suppression then as a continuous infusion for at least 12 h.[22]

2.6. Data collection

A standardized form was used to collect the variables listed in Tables 1–5. Severity and organ dysfunction at ICU admission were assessed using the simplified acute physiology score II (SAPS-II) and the logistic organ dysfunction (LOD) system score.

2.7. Statistical analysis

Quantitative parameters are reported as median (interquartile range [IQR]) and qualitative parameters as number (%). Categorical variables were compared using Fisher's exact tests and continuous variables using Wilcoxon rank-sum tests.

Median (IQR) stay lengths in the ICU and hospital were estimated using the reverse Kaplan–Meier approach. Median (IQR) mechanical ventilation duration was estimated with death as a censoring event.

Receiver-operating characteristic (ROC) curves were plotted to evaluate the performance of TCD and ONSD for detecting NCSE. The area under each ROC curve (ROC-AUC) was calculated and its 95% confidence interval (95%CI) was estimated as described by Delong and Delong. When ROC-AUC was greater than 0.6, several cutoffs were evaluated and the cutoff providing the best compromise between sensitivity (Se) and specificity (Sp) was identified. When several points were at the same distance from the ideal curve (Se = 1 and Sp = 1), priority was given to sensitivity. The positive and negative likelihood ratios (LR+ and LR−) obtained using the optimal cutoffs were calculated.

3. Results

Of 44 patients who met our inclusion criteria during the study period, 6 could not be enrolled because of an inadequate temporal bone acoustic window for TCD monitoring, leaving 38 patients for the final analysis.