Prognostic Value of Somatosensory-evoked Potentials and CT Scan Evaluation in Acute Traumatic Brain Injury

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Background: The aim of this study is to assess whether a complete analysis of all early cortical somatosensory-evoked potentials (SEPs) components and computed tomography (CT) scan features can provide a better prognostic measure than the early cortical component N20/P25 alone, in patients with severe head injury.

Materials and Methods: We studied 81 consecutive patients admitted to intensive care unit with diagnosis of severe head injury. All patients underwent neurophysiological assessment with SEPs and electroencephalography within the first 6 days after trauma. The marginal effect of each variable on Glasgow Outcome Scale score was evaluated by using univariate measures of association. We fit a cumulative logit model by maximum likelihood, and the partial effect of each variable was assessed by likelihood ratio test. We performed variable selection by forward stepwise, according to the Akaike information criterion.

Results: Our final cumulative logit model including SEPs primary complex (pN20/fP20/cP22), SEPs middle latency (N30/P45/N60), and CT scan hypodensity values showed a significantly increased predictive power of Glasgow Outcome Scale, compared with pN20 alone ($P < 0.0001$).

Conclusions: Statistical analysis revealed a highly significant ($P < 0.0001$) improvement in outcome prediction when the model includes a pool of amplitudes and latencies referred to different early-evoked components pN20, pP25, fP20, cP22, N30, P45, and N60, associated to CT scan hypodensity values, compared with the use of the cortical parietal N20/P25 alone.

Key Words: somatosensory-evoked potentials, traumatic brain injury, prognosis, latency, amplitude

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The assessment of posttraumatic coma has been the object of studies since the beginning of the 1950s. The researchers' efforts have not only addressed the analysis of the neurophysiopathologic mechanisms responsible for damage, but also looked for early prognostic indicators, which could be helpful to manage patients with head injury. Somatosensory-evoked potentials (SEPs) have been used in the assessment of traumatic brain injury since the 1970s.[1] In the last 2 decades many authors have described the relationship between evoked responses and outcome basing on the central conduction time, the number of peaks in the SEPs, and a more subjective evaluation of latencies and amplitudes in the early component N20/P25.[1–28] Early components can be detected within the first 100 ms poststimulus. Aim of this study is to extend the analysis to all the early cortical SEPs components to correlate these variables with the Glasgow Outcome Scale (GOS),[29,30] and to verify whether a wider pool of recorded cortical components, associated to computed tomography (CT) scan characteristics, can be a better tool to assess the patient's prognosis than the early components N20/P25 alone. This would be of great value to clinicians to adopt more appropriate early decisions in the management of acute comatose patients.

MATERIALS AND METHODS

We studied 81 consecutive patients (59 males, 22 females; mean age: 26 ± 14 y, range 12 to 64 y), admitted to intensive care unit after a severe head injury. The study did not include patients admitted with brain death diagnosis, nor those who died because of non-neurological complications. The Glasgow Coma Scale (GCS) distribution at admission is shown in Table 1. All the patients, clinically evaluated according to the GCS[31] underwent neurophysiological assessment with SEPs and electroencephalography (EEG) within the first 6 days after trauma. In a subgroup of patients (n = 48) the intracranial pressure (ICP) was also monitored through an intraventricular catheter. Only patients with a GCS score ≤ 8 at the time of neurophysiological assessment were included in

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TABLE 1. Distribution of GCS Values at Admission

Early GCS	No. Patients
8	6
7	15
6	18
5	19
4	14
3	9

GCS indicates Glasgow Coma Scale.

this study. Patients who were moribund at admission (GCS = 3 with bilateral unreactive pupils) were excluded. All patients were intubated and mechanically ventilated. Remifentanil and propofol were given to obtain muscle relaxation and sedation. Patients' body temperature never exceeded the normal range during EP recording sessions. SEPs were generally recorded with minimal sedation. When the patient's conditions required continuous sedation (with no bolus), the dosage of propofol (2 to 3 mg/kg/h) and remifentanil (0.01 mg/kg/h) was compatible with the detection of an EEG rhythm without significant SEPs latency increase or amplitude decrease.

Intracranial mass lesions eventually present were evacuated as soon as possible. PCO_2 was maintained at approximately 35 mm Hg. Arterial pressure was monitored using a radial artery catheter. ICP over 25 mm Hg for >10 minutes was treated with ventricular cerebrospinal fluid drainage, intravenous mannitol, and deep sedation.

During CT scan evaluation, we considered the following parameters to define major and minor CT scan lesion hemisphere. When considering extracerebral and intracerebral hematomas and contusions, the size (mm) of the hemorrhagic lesion and the midline shift were measured. Cerebral edema and hypodense lesions were evaluated by combining both visual inspection and computed measurements using Hounsfield units (HU) (or x-ray absorption coefficients). Six regions of interest were identified on CT scan: frontobasal (f), central (c), parietal (p), temporal (t), occipital (o), subcortical (sc), and mesencephalic (mc). We first hand-draw an area within each of the 6 cortical regions excluding areas with hemorrhage. Then we measured the average HU value within the same areas with a computer. A score from 0 to 3 was assigned to each of the 6 cortical region of interest for each hemisphere:

0 = normal parenchyma (HU > 45),
1 = mild hypodensity lesion (35 < HU < 45),
2 = intermediate hypodensity lesion (25 < HU < 35), and
3 = severe hypodensity lesion (HU < 25).

For statistical analysis, we considered only the hypodense lesion classification, expression of the ischemic secondary damage.

We performed the neurophysiological investigation at the patient's bedside using an electric stimulation of the median nerve at the wrist for 0.2 ms. The impulse was given through 6 mm AgCl disc electrodes, placing the cathode approximately 2 cm proximally to the anode.

The stimulus intensity was considered adequate when causing an evident contraction of the thenar eminence muscles. SEPs were obtained in response to electrical impulses delivered alternately at each median nerve at the wrist. Frequency of stimulation was 3.1 Hz. A total of 500 responses were averaged per trial, and duplicate trials guaranteed reproducibility. We used 4 channels for the standard clinical recordings. Every channel highlights one or more component. Peripheral ipsilateral and contralateral Erb's point channel records N9. Frontal channel (F3/F4-Auricular) records P14, P20, N30, P45, N60. Central channel (C3′/4′-Auricular) records N18, P22, P45, N60. Parietal channel (P3/P4-Auricolar) records N20, P25, N30, P45, N60. Peripheral Erb's point electrodes are designated as EP, and must be placed within the angle formed by the posterior border of the clavicular branch of the sternocleidomastoid muscle and the clavicle, 2 to 3 cm above the clavicle (Erb's point). The active electrode is ipsilateral to stimulation (EPi) and the reference is the contralateral EP electrode (EPc). The peripheral electric impulse was registered at cortical level by 6 electrodes placed on frontal, central, and parietal areas of the scalp bilaterally, according to the 10-20 International System. A band-pass amplified the signal from the 6 channels to a value between 20 and 2000 Hz. Recordings were carried out from both hemispheres to the stimulus point. The earlobe ipsilateral to stimulation is considered an adequate reference for scalp electrodes. We use straight stainless steel needle electrodes for cortical and EP recordings. Both latency and amplitude values of all the cortical components in the first 100 ms of poststimulus temporal investigation were calculated and considered for statistical analysis. Amplitude and latencies of the SEPs were considered pathologic when they exceeded by 2.5 SD the average values obtained with the same method from a control group of 20 healthy adults (13 males, 7 females; mean age 24.7 ± 13.6 y; Table 2). SEPs were recorded at bedside. A total of 500 artifact-free responses were averaged twice in the 100 ms poststimulus epoch to check reproducibility. Latency and peak-to-peak amplitude values were measured for those SEPs components indicated in Figure 1. Amplitude of the main SEPs components was measured between the peaks indicated in Table 2. For convenience, SEPs components have been named by abbreviations, using a prefix to indicate the cortical location (f: frontal; c: central; p: parietal), and a suffix to indicate amplitude (a) or latency (l). For example, fP45a refers to the frontal P45 amplitude. Consciousness of patients was tested daily (1 h after sedatives suspension). SEPs are not affected by sedatives at the dosages used. The mean age of the 2 groups of healthy and head-injured patients was comparable. Outcome was assessed 6 months after the trauma in accordance with the GOS. For statistical analysis, we considered outcome as an ordinal variable with 5 classes.

Statistical Analysis

All the data relative to the cerebral cortical SEPs were reported and assessed separately for the 2 hemispheres. For

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TABLE 2. Average Values and SD of Main SEPs Components

Cortical Area	Amplitudes	Values (A ± SD)	Latencies	Values (A ± SD)
Frontal	N18-P20	0.8 ± 0.4	P20	19.8 ± 1.2
	P20-N30	3.1 ± 1	N30	30.4 ± 1.8
	N30-P45	2.2 ± 1.3	P45	41.5 ± 3.5
	P45-N60	3.5 ± 1.2	N60	58.4 ± 5.7
Central	N18-P22	1.1 ± 0.2	P22	21.4 ± 1.3
	P22-N30	2.3 ± 1.1	N30	30.5 ± 2.2
	N30-P45	2.8 ± 2.2	P45	42 ± 3.9
	P45-N60	4.3 ± 2.1	N60	60.2 ± 4.3
Parietal	P14-N20	2.2 ± 1.1	N20	19.4 ± 1.5
	N20-P25	3.6 ± 0.7	P25	22.1 ± 2.2
	N30-P45	2.9 ± 0.8	P45	42.4 ± 1
	P45-N60	3.6 ± 1.2	N60	61.4 ± 3.2

Amplitude is expressed in mcV, latency is expressed in ms. Amplitude of the main SEPs components was measured between the indicated peaks.
A indicates average; SEP, somatosensory-evoked potential.

each patient, we distinguished functional major-lesion and minor-lesion hemisphere on the basis of N20/P25 amplitude and the presence of intracortical components. The total peak-to-peak cortical amplitude gave the most accurate ranking of functional lesion for the brain hemispheres.[21] The marginal effect of each SEP variable on GOS score was evaluated with univariate measures of association. Associations were assessed by the η^2 measure and tested by using an analysis of variance F test for quantitative variables (age, SEPs data, and CT parameters), and Pearson χ^2 test for the indicator of the higher lesion position.

As our aim was to assess the ability of SEPs and CT to predict GOS scores, which is ordinal, we fit a cumulative logit model. As described by Agresti,[32] this model is typically used when response is an ordinal variable, as GOS is. Under this model, the ratio between the probability to observe a particular GOS score and the probability to observe a lower score depends, through a logit link, on the values of SEPs data and CT parameters. Moreover, it is necessary to consider the joint effect of other related variables.[32]

Cumulative logit model was fit by maximum likelihood, and the partial effect of each variable was assessed by likelihood ratio test. We performed variable selection by forward stepwise, according to the Akaike information criterion (AIC).[33]

RESULTS

In our study we considered 81 patients, suffering from severe cranial trauma, with GCS$\leq$8, an average motor score of 3.3 ± 1.2, and an average age of 26 ± 14 years. Six months after trauma, 40 patients (49.3%) were seen to have an unfavorable outcome, whereas 41 patients

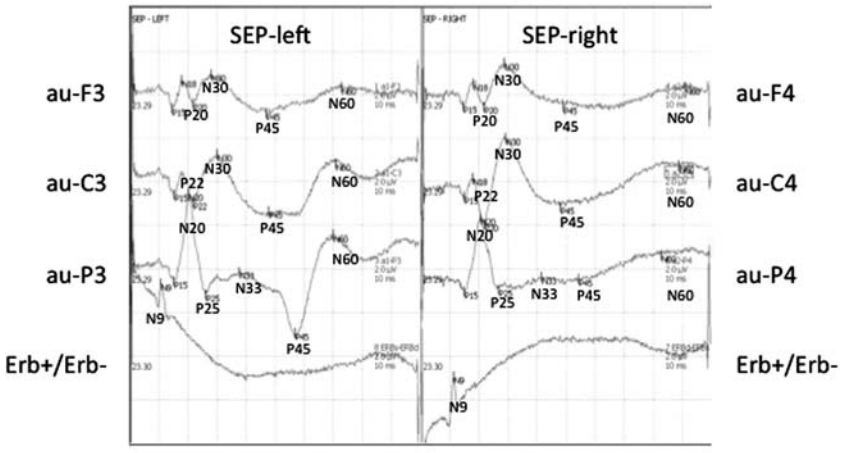

FIGURE 1. Somatosensory-evoked potentials (SEPs) recording sessions from left and right median nerves. P22-N30 is a prerolandic complex generated in the frontal region, which is followed by the N30-P45 complex. They both represent the integrity of the frontal function. The amplitude peak-to-peak complex represents the integrity of the parietal function recorded by electrodes positioned on the parietal scalp. The N60 component follows the N30-P45 complex in the frontal or in the centroparietal regions. It is always missing in deep coma. Its presence during treatment with sedative drugs is highly correlated with favorable outcome. The signals are derived from cortical F3, F4, C3, C4, P3, P4, and peripheral Erb's point bilaterally. Frontal P20-N30, P45-N60, and N30-P45; central complexes P45-N60, P22-N30; and the parietal complexes P45-N60, N20-P25 documented the correct favorable prognosis of patients with a low GCS.

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(50.6%) had a favorable outcome. Table 3 shows the GOS distribution of the 81 analyzed patients, with the frequencies of early GCS scores recorded at admission by final GOS, the relation between GOS and N20, and the relation between GCS and N20.

Supplementary Table 4 shows the marginal association measures for each of the considered variables and *P* values of related tests (Supplemental Digital Content 1, http://links.lww.com/JNA/A16). We included all the available variables in the model: age, position of the major lesion, GCS, the day when SEPs and CT were performed, latency and amplitude of the SEPs components, and CT results for both major and minor lesions. For quantitative variables, such as SEPs components, we considered the η^2 association measure and the connected *F* test. Association between GOS and the categorical variables has been measured through Cramér *V* coefficient and the connected η^2 test. Their value is 0 when the variables are not associated, and 1 when a complete association is observed.

To evaluate whether a wide pool of neurophysiological parameters offers a better prognosis prediction than N20 alone, we included N20 amplitude and latency in the model, selecting the other variables by forward stepwise based on AIC. The summary of the results of the final cumulative logit model is shown in supplementary Table 5 (Supplemental Digital Content 2, http://links.lww.com/JNA/A17). We compared the results of our final model with a simpler model where only GCS, or only CT, or only SEPs where used to predict GOS. Misclassification errors, log-likelihood, likelihood ratio test with respect to the final model, and AIC for each model are included in Table 2.

Twice the log-likelihood of the final 75-parameter model is 152.70, which is significantly lower than the same quantity of the 60-parameter model including amplitude and latency of N20 alone (232.76, $P < 0.0001$). Consequently, also the AIC criterion decreases from 244.76 to 194.70. This confirms that the inclusion in the model of a pool of amplitudes and latencies referred to different waves increases the predictive power of GOS.

Positive estimated coefficients suggest that the cumulative probability starting from the GOS level 1 increases when explanatory variables increase. For example, fixed the level of all other variables, when pN60l has a 1 unit increase, the estimated odds of GOS below any fixed level increases of exp(0.95) = 2.58 times. The middle-latency cortical N60 wave might be expected to have the best correlation with outcome, and therefore be a sufficient parameter to predict GOS. However, a model with this parameter alone has a significantly higher misclassification rate than the complete final model. In our model, we define "misclassification error" any misclassification between 2 contiguous GOS scores (ie, 2 instead of 3, or 4 instead of 3,…). When the misclassification occurs with a gap of 2 or more GOS scores, we define the error as "severe misclassification error" (ie, 2 instead of 4, or 3 instead of 1,…). Our final model can reduce misclassification errors of about 19%, and severe misclassification errors of about 36%, compared with pN20a alone. For a more straightforward clinical use, we calculated a simplified model excluding CT scan. The summary of the results of the simplified final cumulative logit model is shown in supplementary Table 6 (Supplemental Digital Content 3, http://links.lww.com/JNA/A18). Although the misclassification and severe misclassification errors increase of about 4% and 7%, respectively, compared with the complete final model, the outcome predictability is still clinically important (Table 4).

The full prediction matrix of the final model is shown in Table 5.

Cumulative probabilities can describe effects instead of odds ratios. For example, we can consider the effect of the lesion location. At the mean level of all other variables, the probability to die (GOS = 1) is 0.014 if the major lesion occurs on the right side, whereas it is 0.041 if the major lesion is on the left side. As an example with a quantitative covariate, we consider the cP22l on the major lesion side. The lower and upper quartiles of this variable are 3.44 and 4.48. If the major lesion was on the right side, the probability to die changes from 0.015 to 0.006 between these quartiles. If major lesion was on the left side, it changes from 0.416 to 0.018. It is worth noting that if we consider changes of the probability that GOS = 5, cP22l changes from 0.238 to 0.425 if major lesion was on the right side, and from 0.097 to 0.202 if major lesion was on the left side. In the clinical practice, when a simpler method is required, the most predictive variables are pN20 and fN60 amplitudes in the major-lesion hemisphere, and fP20 amplitude, fP45 and cP22 latencies in the minor-lesion hemisphere.

TABLE 3. Relation Between GCS, GOS, and N20

Frequencies of Early GCS Scores by Final GOS

	GOS					
Early GCS	1	2	3	4	5	No. Patients
8	0	0	1	1	4	6
7	0	2	2	1	10	15
6	2	1	5	5	5	18
5	6	3	3	4	3	19
4	3	4	3	0	4	14
3	4	1	0	2	2	9
Total	15	11	14	13	28	81
%	18.6	13.6	17.2	16.0	34.6	100

GOS Versus N20: Absolute Values

	GOS				
N20	1	2	3	4	5
Absent	5	3	0	0	1
Pathologic	7	6	9	6	15
Normal	3	2	5	7	12

GCS Versus N20: Absolute Values

	GCS					
N20	3	4	5	6	7	8
Absent	0	4	3	2	0	0
< 1.2	7	8	9	9	10	4
> 1.2	2	2	7	7	5	2

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TABLE 4. Comparison of Outcome-Predictive Models Based on fN60 Amplitude Alone, and pN20 Amplitude Alone With the Final Model and the Simplified Final Model

Model	Log-Likelihood	AIC	Likelihood Ratio Test With Respect to the Final Model	*P* With Respect to the Final Model	Misclassification Error (%)	Severe Misclassification Error (%)
fN60a alone	232.47	242.47	79.76	< 0.0001	59.26	40.74
pN20a alone	244.09	254.09	91.38	< 0.0001	62.96	44.44
Final model	152.70	194.70			43.21	8.64
Simplified final model	160.82	198.82			46.91	16.05

DISCUSSION

Severe head injury represents a major cause of death and disability. Clinicians are always looking for reliable tools to assess prognosis on these patients. The aim of our study was to identify the clinical and functional parameters with the highest predictive power on outcome. To this purpose, we studied the acute phase of patients' clinical course, taking into account the period within the first 6 days posttrauma. We present the data relative to the acute phase only. Actually, the acute phase is the most important in the patient's management, because it represents the time-window when a reliable prognostic approach can be determinant.[34] At the early stage, the presence of neurosedation hampers clinical evaluation and makes the analysis of background EEG activity and the presence of reactivity unreliable. In our study, as in previous reports,[2,22] increased ICP values particularly in the range of 20 to 35 mm Hg did not prove to be prognostic, being associated with both poor and favorable outcomes. In literature, SEP data are almost always collected from both hemispheres and presented as global values.[6,7,35–37] However, the morphologic and functional damages often differ in the 2 hemispheres. Moreover, the brain damage to the dominant and the nondominant hemispheres has different prognostic implications.[38] For these reasons, we considered and analyzed all the neurophysiological data separately for the 2 hemispheres. Moreover, we distinguished the hemispheres with major and minor functional lesion on the basis of the total SEPs amplitude for each hemisphere.

The SEPs, introduced in the clinical practice since the 1970s, have proved to be the most predictive parameter to assess prognosis, even better than clinical factors like GCS score and age.[2,3,16,23,38–47] Carter and Butt[6] presented a meta-analysis comparing the prognostic value of SEPs, CT, EEG, and GCS photomotor reflex in traumatic brain injury (TBI) comatose patients, concluding that SEPs were the best single prognostic indicator. More recently, Houlden et al[13] confirmed the prognostic SEPs value to predict cognitive and functional outcome. On the basis of these evidences in severe TBI, we can expect 2 very different clinical courses from the first to the second day of coma, depending on the normal or absent SEPs finding. Amantini et al[3] classified parietal N20-P25 amplitude on each hemisphere as normal (N), pathologic (P), or absent (A). Considering both the hemispheres, he defined 3 grades of response. Grade I (NN, NP) had a positive predictive value of 93.1% for "awakening," and 86.2% for good outcome. Grade III (AA) had a positive predictive value of 100% for bad outcome and 72.7% for "awakening." Grade II (PP, NA, PA) was associated with a wide range of outcome. Unfortunately, the majority of severe head-injured patients are classified as grade II. A multivariate analysis including SEPs grading, GCS, and EEG reactivity did not increase the percentage of cases predicted by SEPs alone.

TABLE 5. Full Prediction Matrix of the Final Model

		Final GOS				
		1	2	3	4	5
Predicted GOS	1	11	3	1	0	0
	2	1	2	2	0	0
	3	3	5	7	4	1
	4	0	1	3	1	2
	5	0	0	1	8	25

GOS indicates Glasgow Outcome Scale.

Actually, the presence of poststimulation parietal N20-P25 cortical components is an indicator of favorable outcome. Conversely, their absence is an indicator of negative outcome.[13,23,45,47] Bilateral primary cortical N20-P25 with normal amplitude and latency is predictive for a good outcome, whereas bilateral absence is prognostically unfavorable. Although a continuous monitoring of all early cortical SEPs components is not feasible, it is now possible to carry out continuous parietal N20-P25 monitoring thanks to recent technical advances.[34] The continuous parietal N20-P25 wave shape, amplitude, and latency monitoring can show the progression of secondary damage.[48]

To our knowledge, there are no previous studies analyzing all early cortical SEPs components besides the parietal N20-P25 one. Considering all the early cortical components instead of the parietal N20-P25 alone is useful because the frontal components have their own independent predictive power, and their presence allows a more efficient discrimination of long-term outcome.[38] Almost all the SEPs components, when considered individually, show a significant direct correlation with GOS. Moreover, there is an equal distribution of significant correlations between amplitudes and latencies. Actually, the cortical components of the SEPs, especially their amplitude, are better represented in the hemispheres

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with minor injury. Actually, the less-affected hemispheres have a higher cortical structural integrity, which allows their spatial representation. For this reason, they were used to distinguish between hemispheres with major and minor functional lesion.

Among all the variables that proved to be predictive when considered separately, fN60a and pN20l are significant on GOS in the hemispheres with major lesion. The fN60 component is important not for its specific origin, but because the frontal complexes N30-P45 and the central complexes P22-N30 are always present when this wave is recorded. Painful stimuli were seen to increase the amplitude of N60 wave. This middle-latency cortical component may be an accurate neurophysiological measure for the prognosis of good neurological outcome, because it represents a sensory activation beyond the primary cortex, and it is an expression of thalamocortical and corticocortical networks.[49] Our previous study suggests that the different latencies of the middle-latency cortical SEPs (MLCEPs) may be associated with the activation of different brain areas on fMRI.[50] MLCEPs may represent the integrity of the frontoparietal network involved in the mechanism of the contents of consciousness (awareness).[51] These findings confirm recent evidence showing that cortical connectivity and consciousness recovery can be assessed in patients surviving severe brain injury.[52]

In our experience, this component is always missing in deep coma and during deep sedation. In any event, an N60 wave reliably predicts favorable outcome. In the hemispheres with minor lesion, 3 variables were considered significant: cP22l, cP45l, and, similarly to the major-lesion hemispheres, fN60a. The presence of even 1 single frontal component improves the predictive value especially in terms of outcome. When it is possible to record SEPs components other than pN20, the prognostic power globally improves.

Our results show that the inclusion in the model of a pool of amplitudes and latencies referred to different waves increases the predictive power of GOS. Moreover, a combined analysis of frontal and parietal components of SEPs improves and refines the outcome prediction in severe head injury. This is clinically relevant because the final model allows not only the prediction of awakening, as N20 alone does, but also improves the neurological disability prediction. Serial use of such extended evaluation during the acute phase of TBI is important to detect possible clinical worsening (ie, loss of several middle-latency components during steady-state sedation) and tailor the treatment accordingly. This extended neurophysiological monitoring system offers a more precise picture of the neurological status to be reported to the relatives, and more importantly has significant and obvious implications in the planning of a precocious rehabilitation. The amplitude values of the frontal N30-P45 complex and the prerolandic P22-N30 complex have the main prognostic power. In the clinical practice, when a simpler method is required, the simplified final model without CT scan values shows that the presence of N20/P25 along with the middle-latency components significantly improves the outcome prediction compared with N20 alone. The simplified final model reduces misclassification and severe misclassification errors of about 16% and 28% respectively, compared with the use of pN20 amplitude alone.

CONCLUSIONS

A spatial mapping of all early SEPs components on frontocentral-parietal areas of both major-lesion and minor-lesion hemispheres allows a detailed analysis of outcome prediction and a better prognostic evaluation than using the N20-P25 cortical component alone. Combination of cortical SEPs spatial mapping, continuous N20-P25 monitoring, and CT scan hypodensity evaluation allow a significantly reliable prognostic analysis. This combined SEPs technique can provide a detailed insight on the anatomofunctional brain progression after TBI, and can represent a suitable noninvasive bedside method to monitor treatment efficacy. The complexity of the extended final model would be better managed by specific computer software. However, in the daily intensive care unit setting, a highly significant improvement in outcome prediction can still be easily achieved with a simplified model including only a pool of amplitudes and latencies referred to early-evoked components (fP20, pN20/P25, cP22, N30, P45, N60), compared with the use of the cortical parietal N20/P25 alone ($P < 0.0001$).

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