Can Bispectral Index Monitoring Predict Recovery of Consciousness in Patients with Severe Brain Injury?

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Background: The probability of recovering consciousness in acute brain-injured patients depends on central nervous system damage and complications acquired during their stay in the intensive care unit. The objective of this study was to establish a relation between the Bispectral Index (BIS) and other variables derived from the analysis of the electroencephalographic signal, with the probability of recovering consciousness in patients in a coma state due to severe cerebral damage.

Methods: Twenty-five critically ill, unconscious brain-injured patients from whom sedative drugs were withdrawn at least 24 h before BIS recording were prospectively studied. BIS, 95% spectral edge frequency, burst suppression ratio, and frontal electromyography were recorded for 20 min. The neurologic condition of the patients was measured according to the Glasgow Coma Score (GCS). Patients were followed up for assessment of recovery of consciousness for 6 months after the injury. The studied variables were compared between the group of patients who recovered consciousness and those who did not recover. Their predictive ability was evaluated by means of the P_k statistic. Univariate and multivariate logistic regression was used to model the relation between variables and probability of recovery of consciousness. Cross-validation was used to validate the proposed model.

Results: There were statistically significant differences between the group of patients who recovered consciousness and those who did not with respect to BIS_{max}, BIS_{min}, BIS_{mean}, and BIS_{range}, frontal electromyography, signal quality index values, and GCS_{BIS}. The P_k (SE) values were 0.99 (0.01) for electromyelography, 0.96 (0.05) for BIS_{max}, 0.92 (0.05) for BIS_{mean}, 0.92 (0.06) for BIS_{range}, and 0.82 (0.09) for GCS_{BIS}. The odds ratio for BIS_{max} in the logistic regression model was 1.17 (95% confidence interval, 1.1–1.35). Cross-validation results reported a high-accuracy median absolute cross-validation performance error of 3.06% (95% confidence interval, 1–22.15%) and a low-bias median cross-validation performance error of 0.84% (0.56–2.12%).

Conclusions: The study of BIS and other electrophysiologic and clinical variables has enabled construction and cross-validation of a model relating BIS_{max} to the probability of recovery of consciousness in patients in a coma state due to a severe brain injury, after sedation has been withdrawn.

IN acute brain-injured patients, the probability of recovering consciousness depends on several factors: the degree of central nervous system damage (primary lesion), of paramount importance, the clinical situation on admittance, and complications acquired during the intensive care unit (ICU) stay (secondary damage). Currently, it is difficult to know in advance what neurologic outcome is going to occur, and this is relevant because clinical care to these patients can be better addressed if their outcome can be predicted.[1] A good prognostic indicator does not exist, and predictions are usually based on clinical signs such as the Glasgow Coma Score (GCS).[2,3] Objective assessment of residual cognitive function can be extremely difficult because motor responses may be minimal or undetectable because noncognitive output is possible. Evoked potential studies are of little help in this specific setting, and unprocessed electroencephalography often reports a "global brain damage."[4,5] Owen *et al.*[6] studied covert cognitive processing in patients with a clinical diagnosis of persistent vegetative state, using $H_2{}^{15}O$ positron emission tomography activation. They obtained cerebral blood flow responses in two patients who made a significant recovery some months after scanning.

The Bispectral Index (BIS) of the electroencephalogram is a weighted sum of electroencephalographic subparameters containing time domain, frequency domain, and higher-order spectral information, optimized to correlate maximally with clinical signs of hypnosis.[7,8] In 1996, the US Food and Drug Administration (Rockville, Maryland) cleared the BIS as an accepted measure of the hypnotic effect of anesthetics and sedatives. Prospective clinical trials have demonstrated that maintaining BIS values in the range between 40 and 60 ensures adequate hypnotic effect during general anesthesia while improving the recovery process.[8,9] BIS is also being used for sedation assessment in critically ill patients in the ICU.[10,11] Although BIS has been developed in patients without neurologic disorders, a recently published study[12] found a positive association between higher BIS values and a better neurologic function in critically ill patients.

The hypothesis proposed in this work was that once sedative drugs had been completely withdrawn, the BIS value could give some insight into the "level of brain activity" in patients who, at that moment, were unable to answer to verbal commands because of their deep coma

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state. The goal of this work was to study the relation between the BIS and other variables derived from the analysis of the electroencephalographic signal, with the probability of recovering consciousness in patients in a coma state due to severe cerebral damage.

Materials and Methods

The study was prospectively and consecutively performed in 25 critically ill brain-injured adult patients who did not regain consciousness after sedation withdrawal. These patients were treated in an 8-bed surgical ICU in an 800-bed university hospital. In this ICU, approximately 90 patients with brain injury are admitted per year. All patients included in the study were unconscious and unable to respond to verbal commands, most of them were under pressure support ventilation (mechanically assisted spontaneous ventilation), and all had their trachea intubated. They had not received intravenous sedation for at least 24 h before the study day. The study started in September 1999 and finished in June 2001. All procedures were reviewed and approved by the Institutional Review Board of the Hospital Clinic of Barcelona (Barcelona, Spain).

On admission to the ICU, a number of data were recorded: sex, age, associated diseases, computed tomography scan, type of brain lesion, APACHE II severity score,[13] and therapeutic intervention scoring system.[14] Other data collected during the stay of the patients in the ICU were type of surgery, neurologic invasive and noninvasive monitoring, medical complications, presence of tracheostomy, and cause of death. Days from the injury to the day of study, days under sedation, sedative drugs used, and days without receiving sedation before BIS recording were also registered.

Bispectral Index recording was performed by means of an A-2000® monitor (Aspect Medical Systems, Inc., Newton, MA) using BIS algorithm version 3.4. A three-electrode sensor (BIS® sensor; Aspect Medical Systems, Inc.) was located on the forehead of the healthiest brain hemisphere, which was identified by computed tomography scan, with unilateral bipolar modified frontomastoid montage (Fpz-A_1 or Fpz-A_2, International 10-20 System of electrode placement).[15] Electrode impedance was maintained below 5,000 Ω to ensure adequate signal quality. BIS, 95% spectral edge frequency, burst suppression ratio (BSR), spontaneous electromyographic activity in the frontal area, and signal quality index (SQI) were recorded directly from the output of the A-2000® monitor for 20 min. Although electromyographic activity is defined as the total power (in decibels) of the electroencephalographic signal within 70 to 110 Hz frequency range of the spectrum, it was quantified as a unitless value ranging from 0 to 10.[16] From the BIS values, for each individual recording, estimates of maximal (BIS_{max}),

minimal (BIS_{min}), average (BIS_{mean}), and range of BIS (BIS_{range}) values during the 20-min recording were calculated. Maximal electromyographic value was chosen for calculations when a range was given.

Patients' neurologic status at the moment of study, the day of BIS measurement, was assessed by the GCS (GCS_{BIS}).[2] Patients were followed up for 6 months after the injury or until they recovered consciousness or died. Consciousness recovery was evaluated by measuring the ability of the patient to respond to verbal commands, independently of the degree of disability of each particular patient. Glasgow Outcome Score (GOS)[17] was used to define neurologic patient status on discharge from the ICU, on discharge from the hospital, and at the end of the follow-up period.

Statistical Analysis

Patients were divided into two groups according to their final outcome: those who recovered consciousness (good recovery [GOS = 1], moderate disability [GOS = 2], severe disability [GOS = 3]) and those who had a poor neurologic outcome (persistent vegetative state [GOS = 4] or death [GOS = 5]).

The values of BIS_{max}, BIS_{min}, BIS_{mean}, BIS_{range}, 95% spectral edge frequency, BSR, electromyographic activity, and SQI, as well as the clinical indicators measured on admission (GCS, APACHE II, therapeutic intervention scoring system), and on measurement day (GCS_{BIS}) in the group of patients who recovered consciousness (GOS = 1–3), were compared to the same variables in the group of subjects who did not recover consciousness (GOS = 4 or 5), by means of the Mann–Whitney U test. Statistical significance was considered when *P* was less than 0.05.

The P_k test was used to evaluate the predictive ability of each of the parameters that significantly differed between both groups. The goal was to assess the ability of an indicator to predict an observed response—in our case, the recovery of consciousness. The statistic P_k is a type of nonparametric correlation known as a measure of association that quantifies how well the indicator can predict the observed response. The closer P_k is to 1, the better prediction of the indicator is, whereas a P_k value of 0.5 demonstrates that the indicator is not better than random to predict the observed response. A detailed explanation of the statistic properties of P_k and several applications have been published elsewhere.[18–20]

In an attempt to model the relation between the variables that scored the higher values of P_k, meaning that their predictive capacity was maximal, and the outcome observed (recovery of consciousness), univariate and multivariate logistic regression, using a stepwise method, was used. The objective was to establish a relation between the variables and the probability of recovery of consciousness.

The graphical representation of the relation between

BIS$_{max}$ and the probability of recovery of consciousness was plotted, and estimates of BIS$_{50\%}$ (the value of BIS$_{max}$ associated with a probability of 0.5 of recovery of consciousness) and γ (the parameter defining the slope of the sigmoid curve) were obtained.

Validation of the Proposed Model

To assess the ability of the model in predicting recovery of consciousness and in the absence of a prospective sample of individuals, the method of cross-validation using the "leave-one-out" approach was used.[21,22] For that purpose, the parameters defining 25 submodels of 24 individuals each were estimated using a reparametrization of the logistic regression model as follows:

$$P_i = \frac{BIS_{max_i}^{\gamma_i}}{BIS_{50\%_i}^{\gamma_i} + BIS_{max_i}^{\gamma_i}},$$

where P_i is the probability of recovering consciousness in the ith patient, BIS$_{max}$ is the value of BIS$_{max}$ in the ith patient, BIS$_{50\%i}$ is the estimate of the value of BIS$_{max}$ associated with a probability equal to 0.5 of recovering consciousness, and γ_i is the estimate of the slope of the sigmoid relation, being BIS$_{50i}$ and γ_i the parameters to be estimated for each submodel. Using this approach, 25 submodels were fitted, according to the maximum likelihood criteria; hence, 25 values of BIS$_{50\%}$ and 25 values of γ were estimated, by fitting each submodel to the data of 24 patients each time, using a pooled approach.

The predictions of each submodel were compared to the observed data of the remaining individual. Cross-validation is a convenient method to evaluate the predictive ability of a proposed model when sample size is small and a prospective evaluation unfeasible, and as such, it has been used by different authors.[21,23] This approach also allows us to identify any individual that could have been strongly influential in the model.

Evaluation of the performance was done by comparing the observed probability of recovering consciousness and the predicted probability estimated by each submodel. The observed probability was calculated for each patient who had been left out of the submodel building for validation purposes, by dividing the number of patients who recovered consciousness by the total number of patients in each of three BIS intervals arbitrarily defined: 0–40, 41–70, and 71–100. The predicted probability was estimated by the respective submodel according to the BIS$_{max}$ value of the patient. Performance error was calculated as follows:

$$PE = \frac{P_{obs} - P_{CD}}{P_{CD}} \times 100,$$

where P_{obs} is the value of the observed probability for each patient, and P_{CD} is the value estimated by each one of the 25 "n−1" submodels. From the 25 estimations of performance error, the median value, median cross-validation performance error (MDCV), was calculated. Also, the absolute values of performance error were computed and the median, defined as the median absolute cross-validation performance error (MDACV), was calculated.[21,24]

The MDCV and MDACV can be considered as measures of bias and performance, respectively, of the 25 submodels with respect to the observed probabilities. Confidence intervals were calculated for MDCV and MDACV as described in Campbell and Gardner.[25] The distribution of the 25 estimates of BIS$_{50\%i}$, as well as the 25 estimates for γ_i, was evaluated graphically.

Results

Seventeen men and 8 women were consecutively included in the study. Table 1 summarizes the main demographic characteristics of each patient, including diagnosis, age, GCS at hospital admission, and scores of disease severity, such as APACHE II and therapeutic intervention scoring system. Six patients were chronically hypertensive, 1 had chronic bronchopneumopathy, 1 had a previous liver transplantation, and another was diabetic. Brain injury was due to isolated brain trauma in 8 patients, multiple trauma in 7 patients, subarachnoidal hemorrhage in 8 patients, and stroke in 2 patients.

Five patients had diffuse axonal injury on their computed tomography scan. Eleven patients underwent surgery for evacuating a cerebral hematoma, 2 patients were underwent surgery to clip on an aneurysm, and another 2 patients had an embolization of their intracerebral aneurysms. In 7 of these patients, an external ventricular drainage was placed. All but 3 patients had intracranial pressure monitoring on their intensive care unit admission, and 17 had a continuous monitoring of jugular venous blood saturation.

The most frequent medical complications during the stay in the ICU were infections: 10 patients acquired a purulent tracheobronchitis, nosocomial pneumonia developed in 7 patients, and 4 patients had an episode of bacteriemia. Acute respiratory distress syndrome developed in 5 patients, and 16 patients required vasoactive drugs at some point during their stay. Only four patients received phenytoin treatment during intensive care unit admission. All patients except 4 needed a tracheostomy to accelerate their ventilatory weaning.

Auditory evoked potentials were recorded in 7 patients, and somatosensory evoked potentials (median nerve) were recorded in 8 patients. An electroencephalogram was performed in 8 patients within 1 week of BIS measurements. Results are summarized for each patient in table 1.

Midazolam was used as a primary sedative in 23 patients, and 22 of them also received morphine chloride.

Table 1. Demographic Characteristics

No.	Diagnosis	Age, yr	GCS Admission	APACHE II	TISS	Electroencephalogram/Evoked Potential	Days of Follow Up
1	BT, MT	39	8	11	44	Diffuse encephalopathy	90
2	BT, MT	28	3	15	44	Abnormal AEP and SSEP	180
3	BT, MT	39	3	8	34	Diffuse encephalopathy, normal AEP and SSEP	60
4	S	34	4	13	48	Brain death	2
5	SAH	43	3	17	54	Diffuse encephalopathy	16
6	BT	45	4	26	54		90
7	SAH	53	4	23	63		90
8	BT, MT	38	3	23	46	Diffuse encephalopathy, abnormal cortical AEP, abnormal left SSEP	60
9	SAH	67	11	19	50		30
10	BT	23	3	22	46		23
11	BT	29	3	14	34	Abnormal cortical AEP and SSEP	60
12	BT, MT	39	7	22	41	Normal AEP, abnormal SSEP	40
13	BT	79	11	16	50	Abnormal SSEP	54
14	BT	77	6	29	41	Diffuse encephalopathy	7
15	BT	24	5	18	58		180
16	BT	35	8	12	52	Diffuse encephalopathy Normal AEP and SSEP	20
17	SAH	70	10	12	26		42
18	BT, MT	24	3	15	47		67
19	SAH	38	4	20	44		60
20	BT	25	4	16	36		18
21	S	50	3	20	46		60
22	S	69	4	22	46		20
23	BT, MT	31	3	18	72		180
24	SAH	71	3	25	45	Diffuse encephalopathy	28
25	SAH	76	13	18	50		70

AEP = auditory evoked potentials; BT = brain trauma; GCS = Glasgow Coma Score; MT = multiple trauma; S = stroke; SAH = subarachnoid hemorrhage; SSEP = somatosensory evoked potentials; TISS = therapeutic intervention scoring system.

Fifteen patients received a continuous infusion of clonidine. Table 2 shows the days of sedation, days without sedation before measurement, and days from admission to BIS recording.

The values of the maximal, minimal, mean, and range of BIS, BSR, and 95% spectral edge frequency, as well as SQI and electromyographic activity, are shown in table 3. GCS and the neurologic examination at the time of evaluation are also shown in the same table.

Sixty days (range, 1–180 days) was the median duration of the follow-up period (table 1). The degree of neurologic impairment of patients can be observed in table 2, where neurologic status, according to GOS, at discharge from the ICU, at discharge from the hospital, and at the end of follow-up is described. The severity of the neurologic situation in this study population is supported by the fact that only 2 patients were discharged from hospital, 17 patients were transferred to secondary hospitals to continue their rehabilitation procedure, 5 patients died in the ICU, another died in the hospital general ward, and the last patient died in the referred hospital. The cause of death was brain death or directly attributable to severe brain damage in all patients but one, who experienced acute respiratory distress syndrome after regaining consciousness (therefore, the BIS recorded values in this patient were included in the group of patients who regained consciousness).

No differences were found between the group of pa-

tients who recovered consciousness and the group of those patients who evolved to a vegetative state or died, with respect to demographic characteristics, severity scores, duration of stay in the ICU, days of sedation, and number of days without sedation when recording the BIS (table 4).

As can be seen in table 4, there were statistically significant differences between the group of patients who recovered consciousness and those who did not, with respect to BIS_{max}, BIS_{min}, BIS_{mean}, and BIS_{range}, as well as electromyographic and SQI values. There were also significant differences between both groups with respect to the values of GCS_{BIS}. BIS_{range} values, expressing the degree of variability of BIS during the 20-min period of measurement, showed a wide range in both groups, which was significantly larger in patients who recovered consciousness ($P < 0.05$). SQI was significantly higher in the poor-outcome group ($P < 0.05$), probably related to lower forehead muscle activity in these patients. BSR was also compared between both groups. Even though there was one individual who became brain dead with a BSR of 98%, overall no significant differences were detected between the groups.

The values of P_k (SE) were 0.96 (0.05) for BIS_{max}, 0.92 (0.05) for BIS_{mean}, 0.92 (0.06) for BIS_{range}, and 0.82 (0.09) for GCS_{BIS}. The highest predictive value, based on P_k estimation, was 0.99 (0.01) for electromyography.

Univariate logistic regression identified a relation be-

Table 2. Sedation Days and Neurologic Status Evolution

No.	Days Admission—BIS Day	Days under Sedation	Days without Sedation before BIS	GOS on ICU Discharge	GOS on Hospital Discharge	GOS End Follow Up
1	11	4	7	PVS	PVS	D
2	8	2	6	PVS	MD	GR
3	18	11	7	PVS	PVS	SD
4	2	1	1	D	D	D
5	8	5	3	D	D	D
6	6	4	2	MD	MD	MD
7	13	12	1	PVS	MD	MD
8	15	1	14	PVS	MD	MD
9	9	4	5	MD	MD	MD
10	5	2	3	PVS	PVS	SD
11	10	4	6	PVS	SD	SD
12	10	8	2	PVS	MD	GR
13	4	2	2	MD	MD	MD
14	5	3	2	D	D	D
15	17	11	6	PVS	PVS	SD
16	5	3	2	SD	SD	SD
17	4	2	2	D*	D*	D*
18	10	8	2	PVS	PVS	GR
19	18	17	1	MD	MD	GR
20	10	8	2	PVS	MD	MD
21	4	3	1	MD	MD	GR
22	9	6	3	PVS	D	D
23	10	5	5	SD	SD	SD
24	12	9	3	D	D	D
25	10	5	5	SD	MD	MD

D = dead; D* = death due to acute respiratory distress syndrome (patient recovered consciousness previously to acute respiratory distress syndrome and death, so he is included in conscious patients group regarding Bispectral Index recording results); GOS = Glasgow Outcome Score; GR = good recovery; MD = moderate disability; PVS = persistent vegetative state; SD = severe disability.

tween BIS_{max}, BIS_{mean}, BIS_{range}, GCS_{BIS}, and electromyographic activity with the probability of recovering consciousness. Univariate analysis of spontaneous electromyographic activity showed a strong relation with outcome ($P < 0.0001$). All patients with an electromyographic score greater than 1.5 regained consciousness. All patients who did not recover had electromyographic values of 1.5 or less. Perhaps a higher number of individuals with higher spread of the data would give more information about the relation between electromyographic activity and recovery of consciousness. However, based on our data, it can only be said that electromyographic activity is a good classifier of patients according to their final outcome.

Based on the results of the univariate logistic regression, multivariate logistic regression was applied. When using multivariate logistic regression, only BIS_{max} was significantly incorporated into the model. No other variable, either electrophysiologic or clinical, increased the ability of the model to predict the probability of recovery of consciousness. The odds ratio for BIS_{max} was 1.17 (95% confidence interval, 1.01–1.35). A graphical representation of the model for all the possible values of BIS_{max} is shown in figure 1. As can be seen, the value of BIS_{max} associated with a probability of 0.5 of recovering consciousness was 52.3, and the value of γ was 8.04. A BIS_{max} value of 69 or greater has a probability of at least 0.9 of recovering consciousness.

To validate the model relating BIS_{max} and probability of recovering consciousness, cross-validation was used. Figure 1 shows the graphical structure of the 25 submodels estimated from each subgroup of 24 individuals each. All submodels are close to the graphical representation of the full model.

The performance was evaluated by means of the MDACV for accuracy and the MDCV for bias. As can be seen in figure 2, the results show a high accuracy as reflected in a value of MDACV of 3.06% (95% confidence interval, 1–22.15%) and a low bias with an MDCV of 0.84% (0.56–2.12%). Three individuals in the low-BIS range had observed probabilities of recovering consciousness of 0.33, and in all of them, the respective submodels predicted very low probabilities of recovering consciousness, 0.002 for a BIS_{max} of 24, 0.01 for a BIS_{max} of 30, and 0.0007 for a BIS_{max} of 40.

Another way of comparing submodels to the full model relating BIS_{max} to probability of recovering consciousness is to graphically examine the parameters defining the model ($BIS_{50\%}$ and γ) *versus* the values of $BIS_{50\%}$ and γ estimated in the full model. As can be seen in figure 3, the 25 $BIS_{50\%}$ values are close to the full model value of 52.25, whereas the value of γ for the submodel excluding individual 25 is out of range (23 *vs.* 8), reflecting a more abrupt change in the relation between BIS_{max} and probability of recovery of consciousness when this patient is not included in the full model.

Table 3. Recorded Electroencephalographic Derivative Parameter Results and Neurologic Assessment of the Patients

No.	GCS_{BIS}	Neurologic Examination	BIS Minimum	BIS Maximum	BIS Mean	BIS Range	EMG Range	SQI Range	BSR Range	$SEF_{95\%}$ Minimum	$SE_{95\%}$ Maximum
1	3	Vegetative state	27	30	29	3	1	9	0–3	—	—
2	10	Vegetative state	30	60	45	30	3	10	0	—	—
3	9	Vegetative state	62	97	80	35	9	8	0	15.3	23.4
4	3	Brain death	2	24	13	22	1	10	98	—	20
5	3	Coma	40	50	45	10	0	10	1	—	8.5
6	3	Vegetative state	26	98	62	72	2–8	7–9	2–3	4.8	5
7	8	Vegetative state	40	85	63	45	3	8–10	0	7.6	16.2
8	8	Vegetative state	63	92	78	29	3	9	0	—	14.7
9	8	Vegetative state	38	62	50	24	2–7	10	0	9.5	11.1
10	9	Vegetative state	74	97	86	23	2	8	0	—	26.8
11	6	Vegetative state	56	90	73	34	5	10	0	—	—
12	6	Vegetative state	96	98	97	2	10	9	0	—	28.5
13	6	Vegetative state	50	77	64	27	2	8	1	7.2	10.3
14	7	Coma	41	56	49	15	0	10	0	11.3	12.3
15	8	Coma	38	80	59	42	2–7	8	1	7.7	13.2
16	8	Vegetative state	31	98	65	67	1.5–10	8–10	0	2.8	21.9
17	3	Coma	28	90	59	62	0–3	8–10	0–12	7.2	10.9
18	8	Vegetative state	11	63	37	52	0–3	8–10	0	4	6.4
19	8	Vegetative state	48	92	70	44	3–7	4–7	0	6.1	8
20	8	Vegetative state	40	81	61	41	0–4	8–10	0–21	7.4	22.4
21	9	Vegetative state	49	98	74	49	3–10	7–10	0–2	5.8	18.8
22	8	Coma	34	53	44	19	0	9–10	0–5	6.5	10.4
23	6	Vegetative state	40	70	55	30	0.5–1.5	9–10	0–8	5.7	10.7
24	3	Coma	38	45	42	7	0.5–1.5	10	0	10.8	12
25	10	Vegetative state	30	40	35	10	1.5–2	10	0	7.5	7.9

BIS = Bispectral Index; BSR = burst suppression ratio; EMG = spontaneous frontal electromyography; GCS_{BIS} = Glasgow Coma Score measured the day of the study; $SE_{95\%}$ = 95% spectral edge frequency; SQI = signal quality index.

It can be said that, in terms of accuracy and bias, all the submodels are consistent with the findings of the full model. They have been prospectively validated, each one in a different patient. Although individual 25 seems to be influential in the model, the full model retains its ability to describe the data where it has been built, and

it is also good for predicting the probability of recovery of consciousness given a certain value of BIS_{max}.

Discussion

The main result of our study is that BIS values were significantly different between patients who recovered consciousness and those with poor neurologic outcome

Table 4. Comparison between Both Studied Groups

	No Recovery of Consciousness	Recovery of Consciousness
n	6	19
BIS minimum	36 (2–41)	40 (11–96)
BIS mean*	42.5 (13–48.5)	62.5 (35–97)
BIS maximum*	47.5 (24–56)	90 (40–98)
BIS range*	12.5 (3–22)	35 (2–72)
EMG*	0.5 (0–1)	3 (1–10)
BSR	2 (0–98)	0 (0–21)
SQI*	10 (9–10)	9 (4–10)
$SEF_{95\%}$ minimum	10.8 (6.5–11.3)	7.2 (2.8–15.3)
$SEF_{95\%}$ maximum	12 (8.5–20)	13.2 (5–28.5)
APACHE II	19.5 (11–29)	18 (8–26)
TISS	45.5 (41–54)	46 (26–72)
GCS admission	4 (3–8)	4 (3–13)
GCS day BIS*	3 (3–8)	8 (3–10)
Days of sedation	4.5 (0–9)	4 (1–17)
Days without sedation	3 (1–7)	2 (1–14)
Days of follow up	18 (2–90)	60 (18–180)

Data are expressed as median (range).

* $P < 0.05$.

BIS = Bispectral Index; BSR = burst suppression ratio; EMG = spontaneous frontal electromyography; GCS = Glasgow Coma Score; $SE_{95\%}$ = 95% Spectral edge frequency; SQI = signal quality index; TISS = Therapeutic Interventional Scoring System.
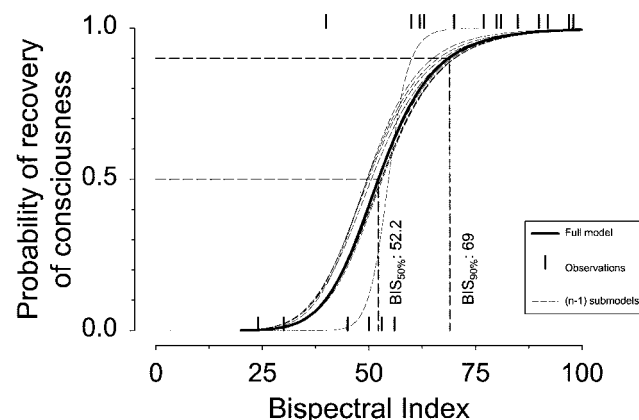

Fig. 1. Graphical representation of the model relating maximal Bispectral Index value (BIS_{max}) and probability of recovery of consciousness. $BIS_{50\%}$ and $BIS_{90\%}$ are the values of maximal Bispectral Index having probabilities of 0.5 and 0.9, respectively, of recovering consciousness. *Vertical bars* on top and bottom of the graph represent the observations for each patient. The 25 (n−1) submodels are represented by the *thin discontinuous lines*.
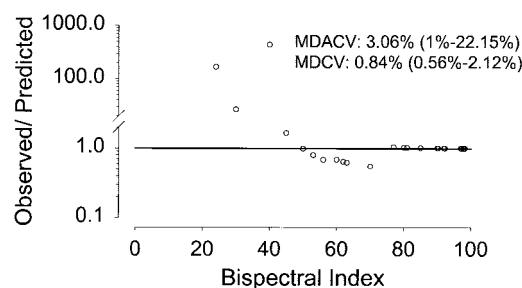
Fig. 2. Graphical representation of the performance of the 25 (n−1) submodels around the observed probabilities of recovering consciousness given a particular maximal Bispectral Index (BIS_{max}) interval. Each *dot* represents the ratio between each observation and the corresponding submodel prediction for the patient who was left out for validation. MDACV = median absolute cross-validation performance error; MDCV = median cross-validation performance error.

(persistent vegetative state or death) and that a model relating BIS_{max} to probability of recovery of consciousness could be built. BIS_{max} and BIS_{mean} values had a high prediction probability, better than traditional clinical measures usually employed in this population, such as the GCS on admission. However, GCS_{BIS} recording was the third variable related to outcome, indicating that this clinical score, measured when the patient is without sedation, can also be useful in predicting neurologic outcome.

Since its introduction in clinical practice, the BIS has been widely used in the operating room as a measure of hypnotic drug effect.[26,27] The development of BIS was entirely focused on obtaining a measure of the hypnotic effects of anesthetic drugs (primarily volatile gases and propofol). As such, the clinical correlation of BIS values in the pharmacologically sedated patient vary with the drug used to provide sedation. Avoiding excessive sedation in critically ill patients has been of increasing relevance in the ICU setting,[28,29] and several authors have proposed the use of the BIS as a tool to control sedation depth.[10,11,30,31]

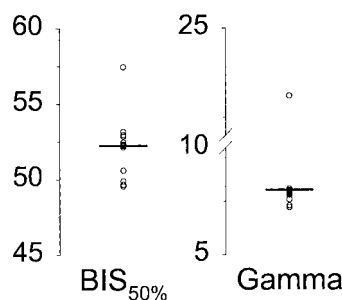The ability of the BIS to provide clinical insight in the absence of hypnotic drugs has not been extensively

Fig. 3. Comparison of the Bispectral Index values associated with the probability of 0.5 of recovering consciousness ($BIS_{50\%}$) and γ estimated for each one of the submodels and the values estimated by the full model. $BIS_{50\%}$ values are very close to the value predicted by the full model except for one subject, the same individual whose estimation of γ was an outlier.

studied. BIS has been shown to correlate closely with reductions in global cerebral metabolic rate produced by anesthetics.[32] Several clinical reports have described how BIS monitoring was used to provide confirmation of brain activity regained during critical intraoperative events including cardiac arrest and resuscitation.[33–35] On the other hand, BIS was the earliest indicator of acute perioperative stroke in a recently published clinical report.[36]

The BIS was not designed to be applied in neurologic patients; nevertheless, its availability in the ICU has led to a number of studies focusing on these patients. Interpretation of BIS in this situation may be complicated if the electroencephalogram also reflects changes in neurologic status caused by critical illness itself. Another limitation of the BIS in this subpopulation relates to its derivation from unilateral, frontal lobe electroencephalographic signals. Gilbert *et al.*[12] were the first to publish a complete article testing the utility of the electroencephalogram as an index of neurologic dysfunction resulting from critical illness. BIS and other electroencephalographic spectral parameters were measured in a population of unsedated ICU patients, and the investigators concluded that better neurologic function was associated with higher values of BIS.

We are aware that a limitation of our study is the fact that we did not have the plasmatic concentrations of sedative drugs during the study day. All sedative drugs were withdrawn at least 24 h, and no patient was diagnosed of acute renal or hepatic failure when BIS values were recorded before collecting the electrophysiologic data. Although it can be argued that in ICU patients, 24 h is insufficient to allow for washout of the sedative drugs, in our case, those patients who could have been at risk of having significant concentrations of sedatives, as patients 4, 7, 19, and 21, all had increased BIS_{max} scores and eventually recovered consciousness.

We performed the exploration during the second week of admission in the majority of patients; none of our patients received sedation from at least 24 h before the BIS recording, and we exclusively included patients who had a delay in awakening. The progress of our patients was followed up until they recovered consciousness or at least for 6 months. In our study, we included different etiologies of the severe brain injury (brain trauma, stroke, and subarachnoidal hemorrhage), although the factors that are known to predict outcome after traumatic brain injury are somewhat different than those that predict outcome after subarachnoidal hemorrhage. We are aware that this could be a limitation of this study, especially with such a small number of patients. In our study, BIS levels were different when patients who recovered consciousness were compared with patients who did not. There was a statistically significant difference ($P < 0.05$) between groups in BIS_{max} and BIS_{mean} values reached. Based on our results, it can be said that

those patients whose BIS_{max} is higher than 52.25 have a probability of recovering consciousness higher than 0.5, and those with BIS_{max} higher than 69 have a probability higher than 0.9.

Cross-validation enabled an initial validation of the model. Based on the performance of the submodels prospectively validated, it can be said that both accuracy and bias are highly satisfactory. There were three cases of poor prediction in the lower BIS value segment, probably because of the small number of individuals in that BIS segment (between 20 and 40). In fact, the model predicted a very low probability of recovering consciousness (approximately 0.1 for BIS < 40), but there was a much higher measured probability (one of three patients with BIS < 40 recovered consciousness). If there had been a larger number of subjects in the low BIS segment and, as expected based in our study sample, a higher number of no recovery, this would have decreased the measured probability of recovery of consciousness, and the prediction of the model would have been more accurate.

One patient deserves special attention because she recovered consciousness even though her maximal BIS values were low. She was admitted in the ICU with a diagnosis of subarachnoid hemorrhage, recovered consciousness, and was able to respond to verbal commands and eat without aid, although her BIS_{max} value during recording was 40. One possibility could be that the patient already had a low-voltage electroencephalogram on baseline.[37] Unfortunately, we have no information about previous electroencephalographic recording or how her electroencephalogram was after she was definitively discharged.

The raw electroencephalogram is not currently used as an outcome predictor in brain-injured patients, other than those with anoxic coma. Diffuse encephalopathy is the most common report in this population. Chen *et al.*[38] found that certain patterns of the raw electroencephalographic signal helped to project 3-month recovery in patients with anoxic coma. All our patients were in "deep coma" when included in the study. Some of them had evoked potential or conventional electroencephalographic studies performed with inconclusive results.

Despite that Theilen *et al.*[39] observed that the fraction of time with a very low-voltage electroencephalographic signal (BSR) soon after severe traumatic brain injury correlated with 6-month outcomes, in our experience, BSR could not help to discriminate which patients would recover consciousness. In fact, we found a high BSR value in only one patient who rapidly became brain dead. Vivien *et al.*[40] have evaluated the accuracy of BIS monitoring for the diagnosis of brain death in severely comatose patients. In their study, the BIS value enabled appropriate scheduling of either electroencephalography or cerebral angiography to confirm brain death.

Vespa *et al.*[41] studied the incidence of seizures after traumatic brain injury. Convulsive and nonconvulsive seizures occurred in 22% of their series. In our study, 4 patients (16%) required treatment with phenytoin for convulsions, but electroencephalography was performed in only 1 patient of this subgroup. In the study of Vespa *et al.*, 16 of 89 patients had an electroencephalographic diagnosis of seizures, these seizures being nonconvulsive in 12 of 16 patients. Nevertheless, in this series, outcome and discharge were not different between the seizure and nonseizure groups. In our study, no seizure activity was detected by electroencephalography in the 8 patients with electroencephalographically documentation.

Another interesting finding of our study is that spontaneous electromyographic activity had a strong prediction probability ($P_k = 0.99$) of consciousness recovering. We do not know the real importance of electromyographic activity in the BIS algorithm, but changes in spontaneous facial muscle activity and its repercussion on BIS values is an issue of increasing concern. Our patients were not under forced–warm air blanket therapy or any other special electrical device known to potentially increase BIS readings.[42] No neuromuscular blocking drugs were used in our patients. Vivien *et al.*[43] showed that the BIS in these patients may be lower with paralysis for an equivalent degree of sedation because of high muscular activity.

Harmel *et al.*[44] suggested that facial electromyographic activity could be used as an objective index of anesthetic effect, muscle relaxation, and level of vigilance. The exclusive motor innervations by the VIIth cranial nerve of facial mimic muscles and, in particular, the multiple connections of the voluntary, involuntary, and autonomic nervous system form the basis of this interesting finding, which has already been the subject of research.[44,45] Surprisingly, in a short communication, Paloheimo[46] observed that the return of facial muscle activity after a hypoxic brain injury was always associated with long-term survival in experimental animals. The author concluded that "the mimic facial muscles express the brain's internal state to the outside world." We cannot rule out the effect of electromyographic activity on BIS values because high-frequency signals, which can come out from frontal or ocular muscle activity, also contribute to the computation of BIS. On the other hand, it is logical to consider that the patients likely to recover consciousness have more facial muscular activity than those who are not likely to recover. We used BIS algorithm version 3.4 for this study, but a newer version of the BIS®, BIS XP®, is specially designed to discriminate and reject artifacts such as patient movement. In the study of Vivien *et al.*,[43] 16 patients were investigated simultaneously with the two monitors (Aspect A-2000® version 2.10 and BIS XP® monitor), and neuromuscular

blockade still induced a significant decrease in BIS values with the new monitor.

To summarize, the study of BIS and other electrophysiologic and clinical variables has enabled us to construct and cross-validate a model relating BIS_{max} to the probability of recovery of consciousness in patients in a coma state due to a severe brain injury, after sedation has been withdrawn. These results would encourage conducting clinical trials in greater populations to validate them.

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