

Prediction of Neurological Outcome Using Bispectral Index Monitoring in Patients with Severe Ischemic-Hypoxic Brain Injury Undergoing Emergency Surgery

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Background: **Predicting outcome from ischemic-hypoxic brain injury can be difficult in patients rushed to the operating room for time-critical emergency surgery. The authors chose to evaluate the prognostic ability of bispectral index (BIS) in this setting.**

Methods: **Twenty-five critically ill, unconscious patients with ischemic-hypoxic brain injury undergoing emergency surgery were prospectively studied. Clinical evaluation, laboratory investigations, BIS, and burst suppression ratio were recorded before and during surgery. Neurologic outcome of the patients was measured according to the Glasgow outcome scale at 30 days after injury, with poor neurologic outcome defined as severe disability or death.**

Results: **The incidence of poor neurologic outcome was 68%. Neither clinical judgment ($P = 0.40$) nor pupillary responses ($P = 0.21$) were predictive of neurologic outcome after surgery. An abnormal BIS trace was strongly associated with poor neurologic outcome, positive likelihood ratio 6.6 (95% CI 1.7–36.4; exact test $P = 0.002$). Some BIS values were significantly different when comparing patients with and without poor outcome: c-statistics for the average BIS and maximal electroencephalographic burst-suppression were 0.80 (95% CI 0.62–0.98; $P = 0.017$) and 0.84 (95% CI 0.68–0.99; $P = 0.007$), respectively. A normal BIS ($P < 0.0005$) but not clinical judgment ($P = 0.16$) could identify a group of patients more likely to survive with a good neurologic outcome.**

Conclusions: **BIS, when compared with clinical judgment and routine laboratory tests, provides useful information that may identify patients with a good chance of recovery after ischemic-hypoxic brain injury requiring emergency surgery.**

SOME critically ill patients with severe ischemic-hypoxic brain injury are emergently transferred to the operating room requiring time-critical life-saving surgery.[1,2] Such patients have uncertain hypnotic requirements and are exquisitely sensitive to anesthetic drug-induced hypotension. For many, the likelihood of neurologic recovery is poor, and modifications to the surgical plan and concerns regarding futility sometimes arise.

A number of clinical signs and neurophysiological tests, including the electroencephalogram, auditory evoked potentials, and somatosensory evoked potentials (SSEP), have been reported to predict neurologic outcome in patients with ischemic-hypoxic brain injury.[3–7] Although SSEP is regarded as a specific and reliable measure of neurologic function and outcome,[3,7] it is a relatively complex tool that requires substantial expertise and has limited utility for most patients in the operating room environment.

Processed electroencephalographic monitoring devices, such as the bispectral index (BIS®; Aspect Medical Systems Inc., Newton, MA), are now being used widely in anesthesia. Given that the isoelectric or burst-suppression electroencephalogram is highly specific for severe irreversible brain injury,[3,7,8] BIS® monitoring may similarly provide a useful measure of cerebral activity in such patients. Several isolated reports support such a contention.[2,9–20]

Thus BIS® monitoring may contribute to the identification of those patients with severe irreversible brain injury who have no realistic chance of a good recovery. Conversely, using existing predictors, some such patients are incorrectly judged to have no chance of recovery and so risk premature termination of active resuscitation and treatment. We therefore planned to evaluate BIS® monitoring in such a cohort of patients.

Materials and Methods

This preliminary study prospectively enrolled sequential patients with suspected severe ischemic-hypoxic brain injury undergoing emergency surgery. Adult male and female patients presenting after arrest or after major hypovolemic or brain trauma and requiring immediate surgery and yet considered by the anesthesiologist to have a high probability of severe irreversible brain injury were identified and recruited to the study. We excluded patients with known or suspected preexisting brain injury or dementia and those suffering an intraoperative cardiac arrest.

Institutional review board approval was obtained before commencement of the study, including a waiver for informed consent from the patient or their next-of-kin.

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Perioperative Management

All patients received their usual perioperative care; enrollment in the study did not affect any clinical decision-making. Preoperative investigations were ordered by nonanesthesiology medical staff and typically included biochemistry, hematology, and arterial blood gas measurements as well as a variable number of imaging modalities (x-ray, computerized tomography) according to availability and urgency of surgery. Some cases were time-critical, resulting in no time being available to undertake any of the aforementioned tests before surgery. Preoperative electroencephalographic or evoked potential monitoring was not done in any of the patients enrolled in the study. In all cases, arterial blood samples were collected intraoperatively for measurement of blood gases and selected biochemistry and hematology indices. Preoperative demographic characteristics, patient medical and surgical history, and operative and anesthetic characteristics were recorded. The durations of severe hypotension and hypoxia were defined as the time when the mean blood pressure of less than 40 mmHg and a pulse oximetry oxygen saturation less than 80%, respectively.

No attempt was made to influence surgical, intensive care unit (ICU), or other neurologic or investigative practices occurring after surgery. All decisions regarding not for resuscitation orders or cessation of treatment were left to the discretion of the ICU and surgical staff, none of whom had knowledge of the BIS data. Any decisions regarding postoperative evaluation of brain function, such as clinical examination, formal brainstem death testing, and radiologic and neurophysiological investigations (including multichannel electroencephalograpm or evoked potentials), were determined according to usual clinical care and in consultation with a neurologist.

Anesthetic Management and Monitoring

On arrival in the operating room, appropriate patient and equipment monitoring was established before induction of anesthesia according to usual practice. All eligible patients were monitored with BIS® (XP version 4.1; Aspect Medical Systems Inc.), with the BIS® electrodes applied in a unilateral frontal-temporal montage according to the manufacturer's instructions, commencing before induction of anesthesia (if applicable). In circumstances where a patient was already sedated or comatose and intubated, such as with transfer from the emergency department or ICU, BIS® monitoring was established before the commencement of surgery.

The anesthesiologists were asked to use their discretion when considering whether to titrate anesthetic drug administration according to the BIS because it is recognized that the utility of BIS is uncertain in such circumstances.[21,22] The following BIS parameters were prospectively defined and recorded: (1) lowest reading persisting for at least 10 min, (2) duration of BIS less than 10 min, (3) highest reading persisting for at least 10 min, and (4) average reading postischemic/anoxic insult. We also recorded the suppression ratio and signal quality index from the monitor output.

The ordering and results of laboratory and radiologic investigations were typically constrained by the need for time-critical and emergency surgery. Most patients had some radiologic investigations, especially chest x-ray, and some trauma patients had an arrival trauma x-ray screen and, less often, computerized tomography scans. All had arterial blood gas estimations immediately after the period of ischemic-hypoxic injury when they had been stabilized as much as possible at the onset of surgery. Other intraoperative blood tests, including repeat arterial blood gases, hematology, and biochemistry, were done after this time. Postoperative investigations were left to the discretion of the treating surgical and ICU staff, often in consultation with a neurologist.

The attending anesthesiologist was asked to record their clinical judgment as to whether or not the patient was expected to have irreversible and severe neurologic injury. This assessment was to be based on the patient's history and duration of hypoxia and/or hypotension, physical examination, and the results of any investigations known at the time of induction of anesthesia. It typically included x-ray, computerized tomography, and the initial arterial blood gas results, but it had to be determined before application of the BIS® electrode. Pupillary size and best light response were evaluated before induction of anesthesia and at the end of surgery; the most favorable pupillary responses were recorded. After commencement of BIS® monitoring and in response to administration of any hypnotic and opioid drugs, they were asked to reconsider their assessment of prognosis. An abnormal BIS recording was defined as either a persistently low BIS and/or electroencephalographic burst-suppression not explained by hypnotic drug administration[21,22] or hypothermia.[11] The anesthesiologist was asked to record the lowest BIS, average BIS, and highest electroencephalographic burst-suppression persisting for at least 10 min, aiming to exclude spurious readings secondary to artifact and/or transient cerebral hypoxia-ischemia. Average BIS was manually calculated, and electroencephalographic burst-suppression data were directly recorded as the suppression ratio output from the BIS® monitor after induction and commencement of maintenance of anesthesia (if employed) until the initial stages of surgery. All anesthesiologists contributing to the study were cognizant of the lack of proven efficacy of the BIS® monitor for prognostication and were strongly advised not to modify their usual clinical care on the basis of the BIS. The surgeon and all other treating staff were similarly advised, and in most cases had no knowledge of the BIS information.

Table 1. Study Population (n = 25)

Male sex		15 (63)	
Age, yrs		42 [24–55]	
Cause of ischemic-hypoxic injury*			
Arrhythmia		9 (36)	
Hypovolemia		14 (56)	
Traumatic brain injury		13 (52)	
Pulmonary embolism		2 (8)	
Systemic embolism		2 (8)	
Cardiac tamponade		3 (12)	
Lowest hemoglobin, mg/ml		82 [64–10]	
Temperature at time of cerebral insult, °C		34.7 [33.4–36.0]	
Duration of mean blood pressure < 40 mmHg, min		12 [8–40]	
Duration of pulse oximetry < 80%, min		5 [0–27]	
Duration of surgery, min		135 [105–270]	
	Induction		Maintenance
Anesthetic drugs			
Midazolam, mg	(n = 12) 5 [0–13]		(n = 4) 6 [5–27]
Propofol, mg	(n = 2) 105 [2–200]		(n = 6) 100 [60–250]
End-tidal sevoflurane, %	—		(n = 8) 0.90 [0.3–1.8]
Fentanyl, μg	(n = 14) 500 [50–750]		(n = 8) 500 [100–500]
Morphine, mg	—		(n = 9) 10 [5–23]
First arterial blood gas results after the ischemic-hypoxic brain injury			
pH		6.99 [6.85–7.13]	
Pao_2, mmHg		73 [49–214]	
$Paco_2$, mmHg		55 [44–68]	
Base deficit, mmol/l		15 [11–22]	
Lowest BIS persisting for ≥ 10 min		5 [0–33]	
Worst suppression ratio		58 [3–95]	
Duration of BIS < 10, min		20 [0–125]	
Average BIS during surgery		28 [7–44]	

Data are median [range] or number (%). * Some patients had more than one insult. BIS = bispectral index; $Paco_2$ = arterial carbon dioxide tension; Pao_2 = arterial oxygen tension.

Primary Outcome

The primary endpoint of interest was the prediction of neurologic outcome measured by the Glasgow outcome scale at 30 days.[23] A poor outcome was defined by a Glasgow outcome scale score of 3 (severe disability), 4 (persistent vegetative state), or 5 (death).

Statistical Analysis

Baseline characteristics were tabulated using appropriate summary statistics, including median range or interquartile range for nonnormal data. Differences between groups were compared using Fisher exact test or Mann–Whitney U test, as appropriate. We used 2 × 2 tables, with poor neurologic outcome indicated by a positive test result. Likelihood ratio, sensitivity, specificity, positive predictive value, and negative predictive value were calculated (see appendix 1). The likelihood ratio was used as our primary index of prognostic ability because it is more stable for changes in prevalence than are sensitivity and specificity.[24] We calculated positive likelihood ratios (sensitivity/1-specificity) to describe the odds that a poor prognosis test result would be expected in a patient with a poor outcome, as opposed to a patient with a good outcome.[7,24] In addition, because clinicians are most concerned about abandoning care in circumstances where outcome could be favorable, we also calculated the proportion of patients with a positive test–indicating a poor outcome – who in fact had a good outcome. We calculated the c-statistic as the area under a receiver operating characteristic curve for selected continuous indices as an additional estimate of predictive ability. For all estimates, we calculated 95% CI. All analyses were done using a Web-based statistical calculator‡ or SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL). $P < 0.05$ was considered statistically significant.

‡ Available at http://statpages.org/; Accesssed July 3, 2008.

Results

We enrolled 25 critically ill patients over a 24-month period (tables 1 and 2). Most patients had severe hypoxemia, hypotension, and metabolic acidosis (table 1). Only 3 patients had received what could be considered a standard dose of hypnotic drug for induction, and a total of 6 patients received greater than 0.5% sevoflurane for maintenance; 12 received a moderate dose (≥ 500 μg) of fentanyl. In total, 17 patients died (n = 16) or had severe disability (n = 1), giving an incidence of poor

Table 2. Summary of Clinical Events in the Study Population of Patients with Suspected Ischemic-Hypoxic Brain Injury Undergoing Emergency Surgery

Patient Sex	Patient Age, yrs	Summary of Clinical Event	Body Temperature at Time of Insult, °C	Duration of Ischemic-Hypoxic Injury,* min	Worst Arterial Blood Gas pH Value	Outcome at 30 Days
Male	54	Unstable coronary syndrome, refractory VF arrest on ward, CPR to theater for salvage CABG	36.5	45	6.70	Good recovery
Male	21	Motorcycle accident with unrecordable BP and GCS 3 at scene, open-book fracture pelvis with hypovolemic shock; fixed, dilated pupils on arrival to ED; rushed to theater	35.6	10	7.08	Death
Male	50	Motor vehicle accident, GCS 3 at scene, intubated without drugs, then arrest with successful CPR; arrived to ED with intact gag reflex; CT: frontal/pterygoid fractures, C1/C2 spinal fractures	32.5	10	7.07	Death
Male	55	Motorcycle accident, multiple fractures (pelvis, femur, tibia), ruptured stomach; hypovolemic shock	34.0	100	6.80	Death
Female	17	Bilateral sequential lung and renal transplant, cardiac arrest on the ward ×3, open CPR, and then emergent cannulation for bypass; severe hypoxemia and acidosis	36.1	15	6.83	Good recovery
Female	34	Motor vehicle accident, GCS 4 at scene; multiple chest, pelvis, and 4-limb injuries; severe hypovolemic shock; fixed, dilated left pupil. Arrival CT: diffuse axonal injury	36.9	0	7.35	Death
Female	40	Motor vehicle accident, GCS 3 at scene, intubated without drugs; multiple fractures, flail chest; severe hypovolemic shock. Arrived to hospital 4 h after injury	35.0	10	7.30	Death
Male	44	Post-heart transplant requiring extracorporeal membrane oxygenation support; worsening hypotension, found to have pericardial collection and widespread intracardiac thrombosis	33.4	60	7.31	Death
Male	43	Assault with chest-stabbing, cardiac arrest at scene, then continuous CPR to hospital with return of circulation; fixed dilated pupils on arrival, x-ray skull fracture, thoracotomy in ED, then rushed to theater	30.0	40	6.59	Death
Male	24	Motorcycle accident *vs.* truck, GCS 3 at scene, then increased to 5, intubated without drugs; normotensive on arrival	34.0	0	6.90	Moderately disabled
Male	47	Motor vehicle accident, sudden loss of consciousness at scene, then GCS 3 at scene; intubated without drugs; normotensive throughout	33.3	12	7.13	Good recovery
Female	33	Fall from fifth story of building onto concrete; GCS 14 at scene then sudden deterioration, intubated on arrival in ED without drugs followed by brief cardiac arrest; emergency thoracotomy/laparotomy in ED, fracture pelvis with internal iliac artery rupture, rushed to radiology for embolization	34.0	5	6.59	Death
Male	17	Pedestrian hit by car; chest and abdominal trauma; skull fracture; CT: complex temporal bone fracture with intracranial air, 3 cm subdural hematoma, loss of grey-white differentiation consistent with hypoxic edema	35.0	0	7.02	Death
Male	23	Jumped from bridge, severe head injury, facial fractures, ruptured bowel, flail chest; GCS 3, intubated at scene; severe hypovolemic shock	34.0	40	6.97	Death

(*continued*)

Table 2. Continued

Patient Sex	Patient Age, yrs	Summary of Clinical Event	Body Temperature at Time of Insult, °C	Duration of Ischemic-hypoxic Injury,* min	Worst Arterial Blood Gas pH Value	Outcome at 30 Days
Male	54	Motor vehicle accident, GCS 3 at scene, intubated without drugs; multiple fractures, ruptured spleen, cardiac rupture with tamponade, severe hypovolemic shock; emergency thoracotomy in ED, massive transfusion	NR	45	6.97	Moderately disabled
Female	29	Out-of-hospital VF arrest, found collapsed by partner, paramedics arrived and commenced CPR after 25 min downtime; recurrent, prolonged VF arrest and emergency CPB	29.0	25	7.06	Good recovery
Female	62	Post-lung transplant cardiac tamponade due to avulsed pulmonary venous anastomoses, leading to hypovolemic cardiac arrest and emergency transfer to theater	NR	29	6.86	Death
Female	86	Known aortic stenosis for revision hip arthroplasty, arrested post-induction and had surgery deferred	NR	4	7.20	Death
Female	55	Traumatic brain injury and severe hypovolemic shock	NR	60	6.89	Death
Male	27	Left ventricular assist device *in situ*, sudden reduction in pump flows and hypotensive arrest on the ward; echocardiographic evidence of extensive mobile thrombus in inflow cannula so rushed to theater; repeat echocardiography noted marked reduction in thrombus size, suspecting systemic embolism and so surgery deferred for neurologic review	36.0	5	7.44	Moderately disabled
Female	19	Motor vehicle accident, GCS 3 at scene, multiple fractures, marked reduction in BP on transfer to hospital, arrested on arrival to ED and rushed to theater	31.8	60	6.99	Death
Male	16	Hit by train, severe head injury with GCS 3, and pulmonary aspiration, followed by VF arrest, stabilized on transfer to hospital and ICU, with severe acute lung injury; following day had rising lactate and suspected ischemic gut for laparotomy	36.0	30	7.07	Moderately disabled
Female	44	Herpes encephalitis with massive pulmonary embolism and cardiac arrest, initially stabilized with thrombolysis and then transferred to theater for embolectomy	34.7	10	6.84	Death
Male	68	Massive anterior myocardial infarction with VF arrest, resuscitated and transferred to another hospital for emergency CABG	37.0	10	7.13	Death
Female	57	Non-ST elevation myocardial infarction with prolonged cardiac arrest 24 hours later, rushed to theater for CABG	37.0	45	6.90	Severely disabled

* Defined as severe hypoperfusion (mean BP $<$ 40 mmHg) and/or hypoxemia (Spo_2 $<$ 80%). BP = blood pressure; CABG = coronary artery bypass graft surgery; CPB = cardiopulmonary bypass; CPR = cardiopulmonary resuscitation; CT = computerized tomography; ED = emergency department; GCS = Glasgow outcome scale; ICU = intensive care unit; NR = not recorded; VF = ventricular fibrillation.

neurologic outcome of 68%. There were 11 patients that, despite ongoing active treatment, died as a result of their extensive injuries within 30 days of surgery; a further 5 patients underwent formal neurologic evaluation and investigation resulting in a diagnosis of extensive and unrecoverable brain injury that led to termination of treatment and withdrawal of support at 1, 4, 8, 15, and 18 days after injury, respectively.

A total of 15 patients (60%) were deemed to have irreversible and severe neurologic injury by their attending anesthesiologist at the onset of surgery. Of these, 8 (32% of total cohort) had fixed and dilated pupils. Neither clinical judgment ($P = 0.40$) nor the absence of pupillary responses ($P = 0.21$) were predictive of neurologic function after surgery in this population (see table 3). An abnormal BIS trace was strongly associated

Table 3. Positive Likelihood Ratio and the Effect of a Change in Prior Probability (Incidence) on Predicted Risk of a Poor Neurological Outcome (Severe Disability, Persistent Vegetative State, or Death) at 30 Days after Injury

Prognostic Factor	Positive Likelihood Ratio (95% CI)	Probability of Poor Outcome after Poor Prognosis (Positive) Test Result (95% CI)		
		60% Prior	75% Prior	90% Prior
Clinical judgment	0.7 (0.5–1.4)	51% (43–68%)	68% (60–81%)	96% (82–93%)
Absent pupillary responses	3.3 (0.7–19.9)	83% (51–97%)	91% (68–98%)	97% (86–99%)
Abnormal BIS	6.6 (1.7–36.4)	91% (72–98%)	95% (84–99%)	98% (94–100%)

BIS = bispectral index.

with poor neurologic outcome, positive likelihood ratio 6.6 (95% CI 1.7–36.4; exact test $P = 0.002$). The effect of a different incidence of poor outcome on the interpretation of likelihood ratios is presented in table 4.

The duration of the ischemic-hypoxic insult and results of arterial blood gas analysis were comparable in patients with and without poor outcome (table 5). Some BIS indices were significantly different between groups (table 5). The c-statistics for the average BIS and maximal electroencephalographic burst-suppression were 0.80 (95% CI 0.62–0.98; $P = 0.017$) and 0.84 (95% CI 0.68–0.99; $P = 0.007$), respectively. Kaplan-Meier survival curves illustrating freedom from poor neurologic outcome in patients judged to have favorable or poor prognosis based on clinical judgment or BIS are presented in figure 1. BIS ($P < 0.0005$) but not clinical judgment ($P = 0.16$) could identify a group of patients more likely to avoid a poor neurologic outcome.

Clinical judgment, the absence of pupillary responses, and BIS could not reliably predict outcome in all cases. False positive (falsely indicating a poor outcome with a positive test) rates, were 24%, 4%, and 4%, respectively; negative likelihood ratios were 1.8, 0.7, and 0.2, respectively. Other prognostic indices are reported in table 4. Six of seven patients with abnormal BIS and absent pupillary responses had a poor neurologic outcome; false positive rate was 4%, and positive and negative likelihood ratios were 6.7 and 0.74, respectively.

Discussion

In this preliminary study, we found BIS® monitoring to be more useful than other indices (duration of insult, clinical judgment, laboratory tests, pupillary responses) in predicting neurologic outcome after a severe ischemic-hypoxic cerebral injury in patients undergoing emergency surgery. An abnormal BIS was associated with a 6.6-fold increased risk of poor neurologic outcome, and a normal BIS was associated with a fivefold increased probability of a good neurologic outcome. Our study population was identified as being at high risk of neurologic injury and one that, although rare in most anesthesiologist's practice, provides a unique set of clinical, ethical, and resource utilization challenges.[3] It must be stressed, however, that the diagnostic utility of BIS should not be extrapolated to nonemergent and lower-risk clinical settings. Furthermore, the BIS® monitor was not designed as a monitor of brain injury, and prognosis after serious hypoxic-ischemic insults should not be determined solely by the BIS® monitor.

Hypoxia and profound hypotension and/or circulatory arrest lead to brain injury once intracellular oxygen stores are depleted[25,26] and such injury can be reflected in the electroencephalograph.[8] Hypnotic drug administration leads to similar changes, with as corresponding reduction in BIS.[21,22] Several studies have confirmed that the BIS correlates well with sedation level and hypnotic drug concentration with a variety of anesthetic regimens in the operating room[22,27,28] and in the ICU.[29] Thus, a persistently low BIS associated with burst-suppression of the raw electroencephalogram in the setting of minimal hypnotic drug administration may indicate severe cerebral dysfunction. There is some information available that supports this conjecture.[8–20,30] The difficulty of anesthesiologists confronted with a patient with suspected brain injury is to interpret a low BIS that could reflect drug-induced hypnosis, brain injury, or both. Most patients in our study received small doses of hypnotic drugs. We defined an abnormal BIS as that which could not be accounted for by hypnotic drug adminis-

Table 4. Other Predictive Indices for a Poor Neurological Outcome (Severe Disability, Persistent Vegetative State, or Death) at 30 Days after Injury

Prognostic Factor	False Positive Rate	Negative Likelihood Ratio	Sensitivity	Specificity	Positive Predictive Value*	Negative Predictive Value*
Clinical judgment	24%	1.88	53%	25%	60%	20%
Absent pupillary responses	4%	0.67	41%	88%	88%	41%
Abnormal BIS	4%	0.20	82%	88%	93%	70%

* These indices are affected by the incidence rate, which in this study population was 68%. BIS = bispectral index.

Table 5. Differences in Factors Potentially Associated with Poor Neurological Outcome (Death or Severe Disability)

Prognostic Factor	Good Outcome (n = 8)	Poor Outcome (n = 17)	*P**
Clinical			
Duration of mean BP < 40 mmHg, min	18 (7–40)	10 (8–40)	0.68
Duration of Spo_2 < 80%, min	5 (1–22)	5 (0–37)	0.86
Arterial blood gases			
pH	7.02 (6.85–7.12)	6.99 (6.85–7.17)	0.95
Pao_2, mmHg	57 (40–182)	84 (55–240)	0.37
$Paco_2$, mmHg	55 (43–59)	55 (44–69)	0.58
Base deficit, mmol/L	14 (12–19)	14 (10–23)	0.71
BIS			
Duration of BIS < 10, min	0 (0–15)	34 (0–170)	0.048
Lowest BIS†	29 (9–38)	2 (0–22)	0.034
Highest suppression ratio†	3 (0–33)	90 (43–100)	0.006
Average BIS throughout surgery	42 (31–53)	17 (3–39)	0.017

Data are median (interquartile range). * Mann-Whitney U test. † Persisting for at least 10 min. BIS = bispectral index; BP = blood pressure; $Paco_2$ = arterial carbon dioxide tension; Pao_2 = arterial oxygen tension; Spo_2 = pulse oximetry oxygen saturation.

tration and/or hypothermia. A very low BIS (< 10) and a high suppression ratio were each strong indicators of probable brain injury. Although the details of the algorithm used to calculate BIS have not been disclosed, we know that for a BIS less than 30 the BIS number is directly related to the suppression ratio (for BIS < 30, the BIS number can be calculated as 50 – suppression ratio/2), such that there is at least 40% burst suppression.[31]

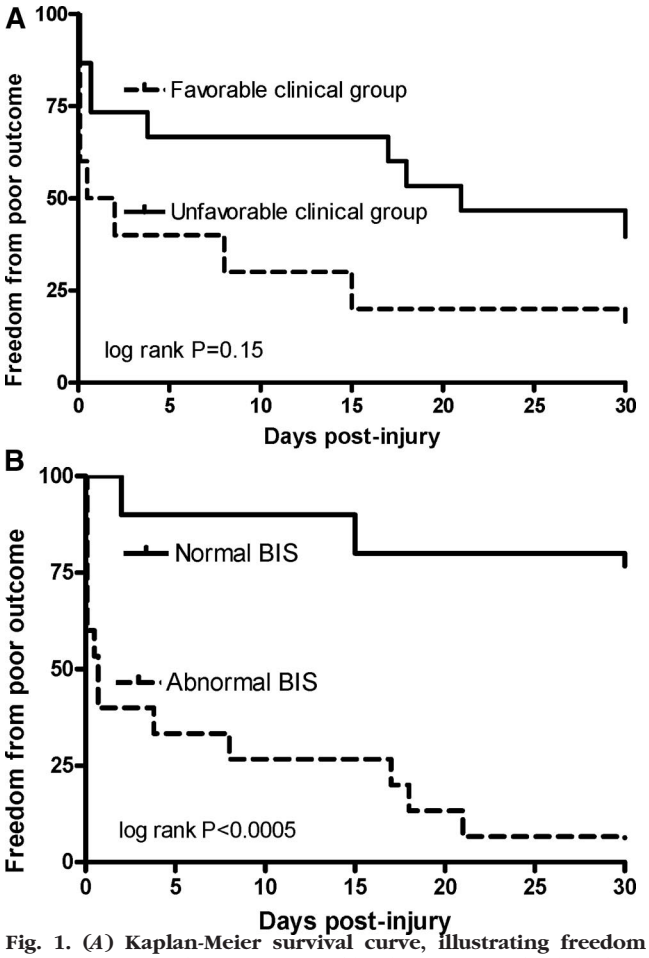

Fig. 1. (*A*) Kaplan-Meier survival curve, illustrating freedom from poor neurologic outcome (death or severe disability) in patients judged to have favorable or unfavorable prognosis on the basis of history, examination, and preliminary investigations. Clinical judgment did not significantly predict outcome. (*B*) Kaplan-Meier survival curve, illustrating freedom from poor neurologic outcome in patients on the basis of presence or absence of normal bispectral index (BIS) parameters. A normal BIS was highly predictive of a good outcome.

The BIS indices that appeared to have the best discriminatory power were the average BIS reading throughout surgery, the extent of electroencephalographic burst-suppression ratio as detected by the BIS® monitor, and a persistent BIS less than 10. The former two indices had good discriminatory power (c-statistic) that were sufficient for prognostication of groups of patients but not sufficiently reliable for an individual patient. This latter point must be emphasized. False-positive predictions of a poor outcome should be especially avoided.[7] In our study, BIS® monitoring (4%) and the absent pupillary responses (4%) had low false-positive rates when compared with clinical judgment (24%). But none were 100% specific; for BIS, about 1 in 25 patients with an abnormal trace will have a good outcome at 30 days. Others have suggested that a false-positive rate of no more than 1% is required before considering outlook as futile.[7] For this reason, we once again emphasize that prognosis after serious hypoxic-ischemic injury should not be determined solely on the information provided by the BIS® monitor. Although pupillary responses had some diagnostic utility, they did not add to that provided by the BIS® monitor.

Conversely, a normal BIS in the postarrest or resuscitation setting provides reassurance of sustained neurologic function,[10,17,20] and it should encourage ongoing active management. In our study, BIS but not clinical judgment or pupillary signs had a significant negative likelihood ratio (0.2; $P = 0.002$); if the BIS trace was normal, then the patient had a fivefold reduction in risk of a poor outcome at 30 days. For example, if a patient was deemed to have a 10% chance of a good outcome (1 in 9 or 0.11 odds), a normal BIS would raise this prediction to about 35%. For clinical judgment and pupillary responses, the predictions are about 4% and 16%, respectively. Thus a normal BIS, in contrast to clinical judgment

and pupillary responses, is more likely to encourage ongoing active resuscitation and treatment.

Both hypothermia and general anesthetics reduce cerebral metabolic rate in a dose-dependent manner.[32] In the setting of profound hypothermia (to 18°C) IV barbiturate has no measurable additional effect on cerebral metabolic rate, indicating barbiturates only affect cerebral metabolism in the presence of neuronal electrical activity.[32] Similarly, an electroencephalographic or BIS response to IV or inhalational anesthesia after suspected ischemic-hypoxic brain injury may indicate preserved neurologic function. This hypothesis deserves further study.

Patients with suspected severe ischemic-hypoxic injury sometimes require time-critical emergency surgery, often without sufficient information on which to make reliable prognoses. At this time, judgment is impeded by a lack of complete clinical and investigatory data and limited time to consult with other clinicians or to integrate the whole clinical scenario. Nevertheless, decisions need to be made and immediate care instituted. Our study clearly highlights the unreliability of the initial clinical assessment and presence or absence or pupillary responses, as has been shown by others.[33] The duration of hypoxia or severe hypotension could not discriminate between those with a good outcomes and those with a poor outcome. Protracted moderate or even severe hypoxia does not necessarily lead to brain injury,[25,26] possibly because of conserved intracellular energy stores and maintenance of autoregulation,[26] but ischemia is poorly tolerated and also aggravates cerebral hypoxia.[26]

A systematic review of 33 studies assessing the prognostic value of clinical, electroencephalographic and evoked potential testing of neurologic function in the ICU setting found absence of pupillary light reflexes, isoelectric or burst-suppression electroencephalograph, and SSEP had the best predictive utility.[7] Early cortical SSEP had the lowest false-positive rate (0–2%). Electroencephalograph recordings with an isoelectric or burst-suppression pattern had a specificity of 100% in five of six relevant studies. They concluded that recording of SSEP is the most useful method to predict poor neurologic outcome in the ICU because evoked potentials are the least susceptible to metabolic changes and drug effects.[7] The authors recommended testing on day 3 after onset of coma because of fluctuating injury response and confounding by residual drug effect. We share this view. However, anesthesiologists are sometimes confronted with emergency surgical patients that appear to have no chance of a meaningful recovery. BIS may have a role in identifying where this may not be the case or expedite additional early assessment in the immediate postoperative period to minimize ICU and other resource use in circumstances where there is no chance of survival.

Gilbert *et al.* [34] measured BIS in 31 conscious, nonsedated, critically ill adult patients in the ICU and found that BIS was significantly correlated with neurologic functional scores, including Glasgow Coma Scale. Similarly, Fàbregas *et al.* [9] studied 25 critically ill brain-injured adult patients who did not regain consciousness after sedation withdrawal in the ICU. Of these, 7 eventually died and a further 13 had moderate (n = 7) or severe (n = 6) disability; 5 had a good long-term recovery. There were statistically significant differences between the group of patients who recovered consciousness and those who did not with respect to maximal, minimal, mean, and range of BIS values. Maximal BIS had good predictive ability for the probability of recovery of consciousness in patients in a coma state due to a severe brain injury. These findings from ICU populations are in agreement with our study of intraoperative patients. Taken together, these findings suggest that BIS monitoring should be continued into the postoperative ICU care environment to assist in the monitoring and evaluation of neurologic function after hypoxic-ischemic brain injury.

Study Limitations

This study only included 25 patients with a variety of sources of brain injury, and therefore had limited study power. The BIS monitor was not designed as a monitor of ischemic-hypoxic brain injury. Also, there are limited performance and utility data in patients undergoing cardiopulmonary bypass.[11] BIS decreases with hypothermia,[11,35] and there have been some reports of technical difficulties preventing interpretation as well as certain artifacts that can falsely increase BIS.[1,36] Such artifacts can result in a misleadingly normal BIS in severe brain injury.[1,18] There are also rare situations where BIS may be falsely low. These include the appearance of paradoxical electroencephalograph delta rhythm and artifacts from the pulsations of temporal artery or from movements of the eyes or head (product literature, Aspect Medical Systems Inc.). An appraisal of the raw electroencephalogram waveform can discern some misleading BIS readings,[37] and this is strongly recommended. Other processed electroencephalogram monitoring devices may also have a role in the prediction of outcome after brain injury.[38,39] Some nonsurvivors may have had satisfactory brain function but succumbed to other injuries. In such cases, the presence of pupillary responses or normal BIS could not be expected to predict death from unrelated causes. It is conceivable that a patient severely disabled at 30 days after injury could eventually have improved neurologic and functional status beyond that time, but such improvements are rare.[7] Although nonanesthetic staff were not made aware of BIS data, it is conceivable that such knowledge could have affected

ongoing care and decisions regarding withdrawal of life support.

Our study suggests that BIS® monitoring provides useful prognostic information in suspected brain-injured patients. It also allows the anesthesiologist to reduce or avoid unnecessary hypnotic drug administration, which may worsen hypotension and the shock state. We must stress, however, that prediction of individual outcome remains problematic and any decision regarding cessation of active treatment must include a consideration of all other relevant clinical information. At the very least, BIS-predicted poor outcome should trigger an early expert neurologic evaluation consisting of clinical, imaging, and neurophysiologic testing as soon as practicably possible. In contrast, a favorable BIS should encourage ongoing resuscitative efforts as neurologic outcome could be good.

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References

1. Myles PS, Cairo S: Artifact in the bispectral index in a patient with severe ischemic brain injury. Anesth Analg 2004; 98:706–7
2. Szekely B, Saint-Marc T, Degremont AC, Castelain MH, Fischler M: Value of bispectral index monitoring during cardiopulmonary resuscitation. Br J Anaesth 2002; 88:443–4
3. Madl C, Grimm G, Kramer L, Yeganehfar W, Sterz F, Schneider B, Kranz A, Schneeweiss B, Lenz K: Early prediction of individual outcome after cardiopulmonary resuscitation. Lancet 1993; 341:855–8
4. Kane NM, Curry SH, Butler SR, Cummins BH: Electrophysiological indicator of awakening from coma [letter]. Lancet 1993; 341:688
5. Signorino M, D'Acunto S, Angeleri F, Pietropaoli P: Eliciting P300 in comatose patients. Lancet 1995; 345:255–6
6. Yingling CD, Hosobuchi Y, Harrington M: P300 as a predictor of recovery from coma. Lancet 1990; 336:873
7. Zandbergen EG, de Haan RJ, Stoutenbeek CP, Koelman JH, Hijdra A: Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. Lancet 1998; 352:1808–12
8. Markand ON: Electroencephalography in diffuse encephalopathies. J Clin Neurophysiol 1984; 1:357–407
9. Fàbregas N, Gambús PL, Valero R, Carrero EJ, Salvador L, Zavala E, Ferrer E: Can bispectral index monitoring predict recovery of consciousness in patients with severe brain injury? ANESTHESIOLOGY 2004; 101:43–51
10. Kluger MT: The bispectral index during an anaphylactic circulatory arrest. Anaesth Intensive Care 2001; 29:544–7
11. Mathew JP, Weatherwax KJ, East CJ, Reves JG: Bispectral analysis during cardiopulmonary bypass: The effect of hypothermia on the hypnotic state. J Clin Anesth 2001; 13:301–5
12. Prabhakar H, Rath GP: Change in bispectral index following intraventricular bleed in neuroradiological suite. Anaesth Intensive Care 2007; 35: 138–9
13. Prabhakar H, Ali Z, Rath GP, Singh D: Zero bispectral index during coil embolization of an intracranial aneurysm. Anesth Analg 2007; 105:887–8
14. Villacorta J, Kerbaul F, Collart F, Guidon C, Bonnet M, Guillen JC, Gouin F: Perioperative cerebral ischaemia in cardiac surgery and BIS. Anaesth Intensive Care 2005; 33:514–7
15. Morimoto Y, Monden Y, Ohtake K, Sakabe T, Hagihira S: The detection of cerebral hypoperfusion with bispectral index monitoring during general anesthesia. Anesth Analg 2005; 100:158–61
16. Welsby IJ, Ryan JM, Booth JV, Flanagan E, Messier RH, Borel CO: The bispectral index in the diagnosis of perioperative stroke: A case report and discussion. Anesth Analg 2003; 96:435–7
17. Billard V: Brain injury under general anesthesia: Is monitoring of the EEG helpful? Can J Anaesth 2001; 48:1055–60
18. Ellenberger C, Diaper J, Licker M, Panos A: Bispectral index and detection of acute brain injury during cardiac surgery. Eur J Anaesthesiol 2007; 24:807–9
19. Gaszynski T: BIS in brain injury. Anesth Analg 2005; 100:293–4
20. Chakravarthy M, Patil T, Jayaprakash K, Shivananda N, Jawali V: Bispectral index is an indicator of adequate cerebral perfusion during cardiopulmonary resuscitation. J Cardiothorac Vasc Anesth 2003; 17:506–8
21. Sigl JC, Chamoun NG: An introduction to bispectral analysis for the EEG. J Clin Mon 1994; 10:392–404
22. Johansen JW, Sebel PS: Development and clinical application of electroencephalographic bispectrum monitoring. ANESTHESIOLOGY 2000; 93:1336–4
23. Jennett B, Bond M: Assessment of outcome after severe brain damage. Lancet 1975; 1:480–4
24. Deeks JJ, Altman DG: Diagnostic tests 4: Likelihood ratios. BMJ 2004; 329:168–9
25. Pearigen P, Gwinn R, Simon RP: The effects of *in vivo* hypoxia on brain injury. Brain Res 1996; 725:184–91
26. Miyamoto O, Auer RN: Hypoxia, hyperoxia, ischemia, and brain necrosis. Neurology 2000; 54:362–71
27. Bruhn J, Bouillon TW, Shafer SL: Bispectral index (BIS) and burst suppression: Revealing a part of the BIS algorithm. J Clin Monit Comput 2000; 16:593–6
28. Carter BG, Butt W, Taylor A: Bilaterally absent pupillary responses: Not always a bad sign. Anaesth Intensive Care 2007; 35:984–7
29. Gajraj RJ, Doi M, Mantzaridis H, Kenny GN: Analysis of the EEG bispectrum, auditory evoked potentials and the EEG power spectrum during repeated transitions from consciousness to unconsciousness. Br J Anaesth 1998; 80: 46–52
30. Gan TJ, Glass PS, Windsor A, Payne F, Rosow C, Sebel P, Manberg P: Bispectral Index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. ANESTHESIOLOGY 1997; 87:808–15
31. DeDeyne C, Struys M, Decruyenere J, Creupelandt J, Hoste E, Colardyn F: Use of continuous bispectral EEG monitoring to assess depth of sedation in ICU patients. Intensive Care Med 1998; 24:1294–8
32. Steen PA, Newberg L, Milde JH, Michenfelder JD: Hypothermia and barbiturates: Individual and combined effects on canine cerebral oxygen consumption. ANESTHESIOLOGY 1983; 58:527–32
33. Vivien B, Paqueron X, Le Cosquer P, Langeron O, Coriat P, Riou B: Detection of brain death onset using bispectral index in severely comatose patients. Intensive Care Med 2002; 28:419–25
34. Gilbert TT, Wagner MR, Halukurike V, Paz HL, Garland A: Use of bispectral electroencephalogram monitoring to assess neurologic status in unsedated, critically ill patients. Crit Care Med 2001; 29:1996–2000
35. Dewandre PY, Hans P, Bonhomme V, Brichant JF, Lamy M: Effects of mild hypothermic cardiopulmonary bypass on EEG bispectral index. Acta Anaesthesiol Belg 2000; 51:187–90
36. Mychaskiw G, Heath BJ, Eichhorn JH: Falsely elevated bispectral index during deep hypothermic circulatory arrest. Br J Anaesth 2000; 85:798–800
37. Barnard JP, Bennett C, Voss LJ, Sleigh JW: Can anaesthetists be taught to interpret the effects of general anaesthesia on the electroencephalogram? Comparison of performance with the BIS and spectral entropy. Br J Anaesth 2007; 99:532–7
38. Nguyen NK, Lenkovsky F, Joshi GP: Patient state index during a cardiac arrest in the operating room. Anesth Analg 2005; 100:155–7
39. Jacobsohn E, De Wet C, Tymkew H, Hill L, Avidan M, Levy N, Bruemmer-Smith S: Use of the Patient State Index (PSI) to assist in the diagnosis of perioperative neurological injury and brain death. J Clin Monit Comput 2005; 19:219–22

Appendix

By convention, it is usual for diagnostic tests to be used to detect disease or predict poor outcome. In this study, a positive test result indicates a prediction of poor neurological outcome, as defined by death or severe disability (see text).

1. Sensitivity (=a/a + c) describes the proportion of subjects with a poor outcome that have a positive test. For example, a sensitivity of 90% indicates that 90% of patients with a poor outcome will have a positive test and that 10% are missed by this test because they have a false negative result.
2. Specificity (=d/b + d) describes the proportion of subjects with a good outcome that have a negative test. For example, a specificity of 80% indicates that 80% of patients with a good outcome will have a negative test and that 20% are missed by this test because they have a false positive result.
3. Positive predictive value (=a/a + b) describes the proportion of subjects with a positive test that have a poor outcome. For example, a positive predictive value of 95% indicates that 95% of patients with a positive test will have a poor outcome, but 5% will not.
4. Negative predictive value (=d/c + d) describes the proportion of subjects with a negative test that have a good outcome. For example,

a negative predictive value of 85% indicates that 85% of patients with a negative test will have a good outcome, but 15% will not.

5. Positive likelihood ratio (=sensitivity/[1 − specificity]; or a/[a + c]/b/[b + d])) describes the odds that a positive test result would be expected in a patient with a poor outcome, as opposed to a patient with a good outcome. For example, a positive likelihood ratio of 4.5 indicates that a positive test increases the odds 4.5-fold for a patient to have a poor outcome.
6. Negative likelihood ratio (=[1 − sensitivity]/specificity; or c/[a + c]/d/[b + d]) describes the odds that a negative test result would be expected in a patient with a poor outcome, as opposed to a patient with a good outcome. For example, a negative likelihood ratio of 0.125 indicates that a negative test decreases the odds to 1/8–fold for a patient to have a poor outcome.

Note that positive and negative predictive values, and positive and negative likelihood ratios are sensitive to changes in prevalence of the disease. The usefulness of diagnostic tests is usually best for midsized probabilities (a prevalence of between 20% and 80%). If a condition is either rare or common, then only a very accurate (both sensitivity and specificity > 95%) test is likely to change posttest probabilities. However, for conditions with midsized probabilities, diagnostic tests can change predicted probabilities substantially, even on the basis of a moderately accurate test.

Appendix. Calculation of Predictive Indices for a Poor Neurological Outcome

	Neurological Outcome	
	Poor	Good
Test result*		
positive	a (“true positive”)	b (“false positive”)
negative	c (“false negative”)	d (“true negative”)

* For each of the diagnostic tests that were studied: (1) clinical assessment, (2) pupillary responses, and (3) abnormal bispectral index.

Prevalence is another word for prior or pretest probability. Prevalence can be multiplied by the likelihood ratio to estimate the posttest probability of a poor outcome. If the chances of a poor outcome are believed to be, for example, 75% (*i.e.* odds of 3 to 1) and a positive likelihood ratio is 4.5, then a positive test will increase the odds to 13.5 to 1, corresponding to a posttest probability of about 93%.

A negative test result should rule out a poor outcome. Using a prior probability of 25% (*i.e.*, odds of 0.33 to 1), and a negative likelihood ratio of 0.125, then a negative test will decrease the odds to 0.04 to 1, corresponding to a posttest probability of about 4%.