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Original Article

Bi-spectral index values in predicting severity and prognosis in patients with diffuse axonal injuries

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Abstract: Objective: Diffuse axonal injuries (DAI) are one of the leading causes of vegetative states and deaths in patients with brain trauma. The current study aimed to investigate the effects of bi-spectral index (BIS) values on prognosis in patients with DAI. Methods: A total of 88 patients with DAI undergoing BIS monitoring were evaluated using Glasgow coma scores (GCS). Serum neuron specific enolase (NSE) and S100 protein levels were assayed within the first 3 days after admission. Patients were divided into 2 groups, the survival group (n = 48) and death group (n = 40). Correlation between BIS and GCS and S100 protein and NSE was detected using Pearson's correlation analysis. Student's t-tests or Chi-squared (χ^2) tests were used for single variable analysis. Univariate logistic regression analysis was used to explore the correlation of DAI patient mortality with pupil anomalies, BIS, NSE, S100, and GCS. The value of BIS in predicting prognosis of DAI patients was tested using receiver operating characteristic (ROC) curves. Results: BIS was shown to be positively correlated with GCS ($r = 0.534$, $P < 0.001$) and negatively correlated with serum NSE ($r = -0.592$, $P < 0.001$) and S100 levels ($r = -0.595$, $P < 0.001$). When grouped by outcomes within 28 days post-injury, DAI patients that survived displayed higher BIS values than those that died ($t = 8.890$, $t < 0.001$). Logistic regression analysis revealed that high BIS was an independent protective factor, showing the greatest impact on prognosis of DAI patients (OR = 0.472, P = 0.003). ROC curve results showed that the area under the curve was 0.902 ± 0.033 and the optimal cut-off value of BIS was 60. Conclusion: BIS is beneficial for prognosis evaluation of DAI patients.

Keywords: Bi-spectral index, diffuse axonal injury, severity, prognosis

Introduction

Diffuse axonal injury (DAI) is a significant pathologic feature of traumatic brain injuries (TBI) [1]. DAI accounts for 28%-42% of severe TBI and is frequent result of vehicle accidents and falls [2]. It has a mortality rate of 42%-62%. Of those that survive, 30%-40% live with severe disabilities or remain in a persistent vegetative state [3]. Significant progress has been made in understanding DAI pathogenesis. However, clinicians are still challenged by difficulties in predicting severity and prognosis and monitoring pathologic conditions for patients with DAI [4].

Bi-spectral index (BIS) is a weighted sum of multiple electroencephalographic (EEG) subparameters. It indicates the depth of sedation and levels of brain consciousness, ranging from 0 to 100. A BIS value of 100 indicates complete wakefulness, while 0 indicates the absence of brain electric signals and complete suppression of activity in the cerebral cortex. Values of 60-85 and 40-60 are characteristic of states of deep sleep and general anesthesia, respectively. BIS of less than 40 indicates suppressed brain activity [5]. BIS has been traditionally used for evaluation of the depth of anesthesia and consciousness during operations [6]. More recently, BIS monitoring has been used for coma assessment and prognosis evaluation of patients undergoing cardiopulmonary resuscitation in Intensive Care Units (ICU) [7, 8]. Clinical application of BIS monitoring in DAI patients has not yet been reported. The current study evaluated the value of BIS monitoring on the prognosis of patients with DAI.

Table 1. Relationship of BIS with GCS, serum NSE, and S100 levels

Factors	GCS	Serum NSE level	Serum S100 level
R	0.534	-0.592	-0.595
P value	< 0.001	< 0.001	< 0.001

Note: BIS, bi-spectral index; NSE, neuron specific enolase; GCS, Glasgow coma score.

Materials and methods

Patients

A total of 88 patients with DAI were admitted to Yancheng City No.1 People's Hospital, between January 2015 and January 2016. Patients were divided into 2 groups according to outcomes at 28 days post-injury, including the survival group (n = 48) and death group (n = 40).

Inclusion criteria: 1) Definite evidence of brain trauma, fitting the diagnostic criteria of DAI [9]; 2) Hospitalization within 6 hours, with immediate CT exams; 3) Glasgow coma scores (GCS) ≤ 8 when received; and 4) No manifestations that called for surgical intervention.

Exclusion criteria: 1) Patients with prefrontal lobe defects; 2) Brain diseases, such as epilepsy; 3) Allergies to the electrode slice of BIS; 4) Patients that underwent surgery later during hospitalization due to delayed traumatic intracranial hemorrhages; 5) Patients with a history of brain trauma and chronic brain lesions; and 6) Patients with severe multiple injuries. The current study was compliant with the ethical standards of medicine practice and was approved by the Ethics Committee of Yancheng City No.1 People's Hospital. Informed consent was obtained from all patient families.

Data collection and BIS monitoring

Profiles were established for the DAI patients by collecting characteristic data, including gender, age, cause of injury, pupil changes, and outcomes (survival or death) at 28 days post-injury. BIS monitoring was performed within the first 3 days after admission, as previously described [10]. No patients received any sedatives before or during BIS monitoring. Continuous BIS monitoring was performed for 12 hours. BIS values were recorded every 30 minutes. For each recording, BIS values with a signal quality index (SQI) ≥ 80 and electromyographic (EMG) artifacts ≤ 45 dB were used to calculate the mean value of BIS. GCS was recorded during BIS monitoring. At the same time, serum neuron specific enolase (NSE) and S100 protein levels were examined using electrochemiluminescence immunoassays.

Statistical analysis

Statistical analysis of collected data was performed with SPSS 19.0 software. Results are expressed as mean ± standard deviation ($\bar{x}$ ± sd). Continuous variables between the two groups were compared by independent t-tests. Categorical variables were analyzed using Chi-squared (χ^2) tests. Pearson's correlation analysis was used to detect any correlation between BIS and GCS and serum NSE and S100 levels. Receiver operating characteristics (ROC) curves were established to evaluate the significance of BIS values in prediction of the prognosis of patients with diffuse axonal injuries, based on areas under the curve. Univariate logistic regression analysis was used to investigate factors predicting prognosis in patients with diffuse axonal injuries. Variables for multivariate logistic regression were selected by the forward step method, with exclusion criteria set at $\alpha = 0.10$ and inclusion criteria set at $\alpha = 0.05$. $P < 0.05$ indicates statistically significant differences.

Results

Patient characteristics

A total of 88 patients with DAI were included in this study. The average age was 44.1 ± 15.3. There were 61 males and 27 females. Causes of injury included auto accidents (61 cases), falls (20 cases), and assaults (7 cases). According to patient prognosis, they were divided into the survival group and death group.

Correlation between BIS, GCS, serum NSE, and S100 levels

Results showed that, of the 88 DAI patients, there was a significant positive correlation between BIS and GCS ($r = 0.534$, $P < 0.001$) and a significant negative correlation between BIS and serum NSE ($r = -0.592$, $P < 0.001$) and S100 ($r = -0.595$, $P < 0.001$). See **Table 1**.

Prognosis of DAI across patient characteristics

As shown in **Table 2**, differences in gender, age, and cause of injury between the two groups

Table 2. Analysis of variables affecting prognosis of DAI

Variable	Survival (n = 48)	Death (n = 40)	t/χ^2	*P* value
Age (year)	45.8 ± 16.6	42.0 ± 15.0	1.132	0.263
Sex			0.024	0.899
Male	33	28		
Female	15	12		
Cause of injury			1.581	0.455
Auto accidents	34			
Falls	9	11		
Assaults	5	2		
Pupil anomaly			11.973	0.001
Yes	21	32		
None	27	8		
BIS	58.97 ± 10.84	30.52 ± 17.65	8.892	< 0.001
NSE (μg/L)	30.53 ± 11.52	63.52 ± 17.43	-10.623	< 0.001
S100 (μg/L)	1.11 ± 0.31	2.13 ± 0.54	-10.540	< 0.001
GCS	5.67 ± 1.19	3.90 ± 0.84	8.128	< 0.001

Note: DAI, diffuse axonal injury; BIS, bi-spectral index; NSE, neuron specific enolase; GCS, Glasgow coma score.

Table 3. Assignment of variables

Variable	Assignment
Pupil anomaly	1 = Yes; 2 = None
BIS	BIS ≤ 46 = 1; BIS > 46 = 2
NSE	NSE ≤ 45 = 1; NSE > 45 = 2
S100	S100 ≤ 2 = 1; S100 > 2 = 2
GCS	GCS ≤ 5 = 1; GCS > 5 = 2

Note: BIS, bi-spectral index; NSE, neuron specific enolase; GCS, Glasgow coma score.

were statistically insignificant (P = 0.899; P = 0.263; P = 0.455). However, differences in pupil changes, BIS, GCS, NSE, and S100 levels were statistically significant (P = 0.001; P < 0.001; P < 0.001; P < 0.001; P < 0.001).

Logistic regression analysis between DAI prognosis and multiple variables

Variables concerning pupil change, BIS, NSE, S100, and GCS were included in univariate logistic regression analysis. Continuous variables, such as BIS, NSE, S100, and GCS, were changed to ranked data according the median. Assignments of variables are shown in **Table 3**. Results showed that BIS (OR = 0.472, P = 0.003) was a risk factor for predicting prognosis of DAI patients. Differences were statistically significant. Coefficients of this logistic regression model are shown in **Table 4**, indicating the probability of poor prognosis $p = 1/(1 + e^{-5.775+0.127x})$.

ROC curve analysis

ROC curves are shown in **Figure 1**. The area under the curve was 0.902 ± 0.033. Sensitivity was 49.75% and specificity was 90.18%. The optimal cut-off value of BIS was 60, indicating that BIS may be a potential efficient prognosis factor for DAI patients.

Relationship of BIS values with prognosis of DAI patients

According to BIS values, patients were divided into the BIS ≤ 60 group (n = 60) and BIS ≥ 60 group (n = 28). There were 24 survival patients in the BIS < 60 group and 24 survival patients in the BIS > 60 group. There were significant differences between the two groups (P < 0.001), as shown in **Table 5**.

Discussion

Bi-spectral index (BIS) is a statistic based on several sub-parameters of the electroencephalogram (EEG). It has been established that BIS is an independent variable in the prognosis of severe brain trauma, with higher BIS correlating significantly with better prognosis. BIS values ≥ 60 typically suggest a good prognosis [11, 12]. To the best of our knowledge, BIS monitoring has not yet been examined for its efficacy in clinically evaluating prognosis of DAI. The current study showed that BIS is positively correlated with GCS and negatively correlated with serum NSE and S100 levels. When grouped by prognosis, DAI patients that survived displayed a much higher BIS than those that did not survive. Logistic regression analysis revealed BIS as an independent risk factor, showing the greatest impact on prognosis of DAI.

Changed pupil conditions are common for DAI patients, including dilation on one side or both, absent or delayed response to light, and a needle-shape, along with other types of deformities. These changes could suggest more traumatic DAIs, in which damage to the hypothalamus and brain stem have occurred. As

Table 4. Logistic regression analysis between DAI prognosis and multiple variables

Variable	Regression coefficient	OR	Standard Error	Wald	*P* value
Pupil change	3.761	1.357	2.185	2.964	0.085
BIS	-0.127	0.472	0.042	8.929	0.003
NSE	0.118	1.289	0.087	1.852	0.174
S100	1.973	1.415	1.584	1.551	0.213
GCS	-0.400	1.308	0.670	0.356	0.551

Note: DAI, diffuse axonal injury; BIS, bi-spectral index; NSE, neuron specific enolase; GCS, Glasgow coma score.

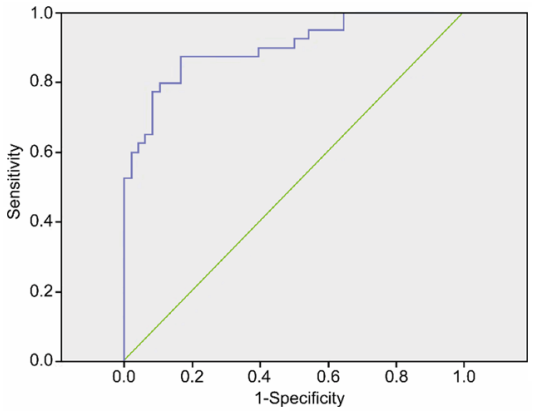

Figure 1. Prediction of death among DAI patients based on the BIS value of the ROC curve. DAI, diffuse axonal injury; BIS, bi-spectral index; AUC: area: 0.902; 95% confidence interval: 0.837-0.967; standard error: 0.033.

a result, poorer prognosis may be given [13]. According to statistical analysis, higher rates of pupil changes were found in the group of patients that died. However, logistic regressive analysis failed to indicate pupil changes as an independent variable, likely due to the lumped accounting of single and both side pupil-change cases performed. Present results are consistent with previous studies [14].

Serum S100 and NSE are important neurobiological markers in brain trauma assessment and prognosis [15]. S100 and NSE typically exist in glial cells and neurons, respectively. Thus, they are extremely low in blood. Increased levels of S100 and NSE in the blood stream could be caused by the breakage of the blood brain barrier as a result of brain trauma. Levels have been positively associated with severity of damage. Higher S100 and NSE levels are indicative of poorer prognosis for patients [16-18]. Results from this study showed a negative correlation between values of the above markers and BIS. Patients that did not survive had much higher levels of NSE and S100 than those that survived. Logistic regression analysis did not show independence of serum NSE and S100 as variables in the prognosis of DAI. This may be due to the small size of samples selected. Future studies should employ a larger number of samples, dynamically monitoring the trends of NSE and S100.

Glasgow Coma Scores (GCS) is a main index for assessment and prognosis of brain trauma [19, 20]. Immediate comas are typical of DAI patients after the initial injury. The typical coma duration is lengthy and GCS is typically low [21, 22]. In this study, patients that did not survive had much lower GCSs than those that did survive. However, logistic regression analysis did not indicate GCS as an independent variable in the assessment and evaluation of DAI, likely the result of the subjective nature of GCS. Even for the same patients, GCS can vary among different examiners. It is also subjected to factors such as the adoption of tracheotomies and tracheal intubation, as well as administration of sedative drugs and observation of facial edema, in severe DAI cases. As a result, there remains great uncertainty in using GCS as an indicator of DAI severity and as an input for prognosis. In early stages, serum NSE and S100 can be valuable indicators of trauma severity, providing sound prognoses. However, due to the inherent lag of results and the frequency of blood work needed, real time continuous monitoring is often impractical. BIS is a more intuitive and objective alternative for DAI monitoring, with wider application. For example, in coma patients where verbal cues are not usable, BIS provides direct monitoring of electroencephalogic activity. In addition, BIS is non-intrusive, easy to operate, and allows for continuous monitoring. Present results are consistent with previous study results [23, 24].

In conclusion, BIS is an objective index beneficial for early stage evaluation and prognosis of DAI. Therefore, it is worthy of extensive clinical application. However, there were some limitations to the current study. This study included a small sample size and it was a single-center trial. Moreover, this study did not indicate BIS changes at different time points, subdivisions of BIS within 24 hours, and influence of DAI progression on BIS. Additional studies are neces-

Table 5. Relationship of BIS with prognosis of DAI patients

Prognosis	BIS < 60 group (n = 60)	BIS > 60 group (n = 28)	χ^2	P
Survival	24 (40.00%)	24 (85.71%)	16.090	< 0.001
Mortality	36 (60.00%)	4 (14.29%)		

Note: BIS, bi-spectral index; DAI, diffuse axonal injury.

sary to collect more cases. Prospective multicenter follow-up controlled trials are required for further investigation.

Disclosure of conflict of interest

None.

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