

Combined BIS and Serum Neuron-Specific Enolase in the Predictive Value of Acute Cerebral Function Change in Coma Patients

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Abstract:

Objective: To evaluate the prognostic value of the bispectral index (BIS) and neuron-specific enolase (NSE) in the acute cerebral function change in coma patients.

Methods: In research studied total 28 patients selected which classified under coma Patients. Patients defined as unconscious, unresponsive, or having a Glasgow coma scale score (GCS) ≤ 8 were considered as comatose in studies. Among them, 13 male patients, 15 female patients in the age between 48 to 92 years old, (72.10 \pm 11.35) years old. The BIS values were recorded and the serum NSE was measured at 24 hr, 72 hr and one week respectively after ICU admission. Neurological outcome was classified according to the Pittsburgh cerebral performance category (CPC 1 to 5).

Result: The prognosis of the group (cpc1-3) Age (60.36 \pm 6.46) is lower than the poor prognosis Group (cpc4-5) (79.7 \pm 5.94) ($P < 0.05$), the difference between the two groups of sex ratio is not statistically significant. BIS values at 24hr, 72hr and one week BIS were recorded in two groups of patients and find-out that there was no statistically significant difference in the 24h BIS value of both groups [(Cpc1-3: (58.63 \pm 12.10) vs. Cpc4-5: (53.76 \pm 14.27)), the BIS value at 72 hours of good prognosis group was higher than bad prognosis group [(cpc1-3: (68.3 \pm 14.2) vs. Cpc4-5: (56.7 \pm 25.5)) is significantly Higher ($P < 0.05$), and the BIS value at one week in good prognosis group was significantly higher than bad prognosis group [cpc1-3: 84.18 \pm 13.2] vs. Cpc4-5: (63.1 \pm 27.3)] ($P < 0.05$). NSE Value, There was no significant change between the two groups under 24hours [(cpc1-3: (63.5 \pm 27.1) vs. Cpc4-5: (71.2 \pm 39.6)), after 72 Hours, the prognosis of a good group of NSE significantly decreased ($P < 0.05$) [(Cpc1-3: (53.2 \pm 19.6) vs. Cpc4-5: (87.7 \pm 49.5)) after one week, the prognosis of a good group of NSE level is also lower than the prognosis of the poor group ($P < 0.05$) [(Cpc1-3: (46.1 \pm 20.7) vs. cpc4-5 96.3 \pm 37.0)). the cut-off value of NSE 47.62 ng/ml, sensitivity 79%, specificity 85%. In one week, NSE values were 38.6 ng/ml, the sensitivity degree is 86%, the specificity is 99% and AUC at 24, 48 and 72 hours is 0.59, 0.83 and 0.98 respectively.

Conclusion: The values of BIS and NSE were effective prognostic indicators for the acute cerebral function change in coma patients.

Keywords: Neuron-specific enolase, Bispectral index, Neurologic outcome, cerebral performance category and Glasgow coma scale.

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I. Introduction

Nowadays, advance and modern technology are uses for accurate and precise result in brain resuscitation but still rate of brain resuscitation in coma patients recovery results are underline although, At present, the commonly used detection methods are neurological clinical evaluation, EEG, somatosensory evoked potentials, neuroimaging and so on, but often there are not timely, interference factors, bedside examination difficulties and other shortcomings, it is possible to find some serum biomarkers combined with a continuous test method at the bedside to determine the neurological function prognosis for brain resuscitation in coma patients.

The aim of study was to investigate the prognostic value of serum neuron-specific enolase (NSE) and BIS in predicting outcomes in acute cerebral function change in coma patients. Neuron-specific enolase can be used to predict the neurological prognosis of coma patients and it was initially used to monitor the depth of anaesthesia in patients with general anaesthesia, and is also currently being applied to clinical monitoring of patient's consciousness state and neurological impairment levels and the indicator quantification, can be continuously monitored by the bedside. Bispectral Index Scale (BIS) a parameter derived from a mathematical analysis of the EEG, depicts brain activity. BIS values range from 0 to 100: 100 indicates a fully awake adult

and 0, total electrical silence of the brain. BIS values between 40 and 60 are considered to be indicators of adequate sedation. NSE is a two-dimer isozyme of Enolase, which is in the neuronal and neuroendocrine cell cytoplasm, and if the neurons are necrotic, the NSE will leak out to the cells, and the concentration of body fluid can be increased. Several studies have confirmed that NSE can be used to predict the prognosis of value for brain resuscitation in patients during unconscious, unresponsive condition and also the most important advantage of biomarkers is that their levels are not disturbed by sedation or neuromuscular blockers, and can usually be applied in the 1st to several days after cardiac arrest. The results showed that the 72hr and one week NSE levels in the patients with good prognosis were significantly lower than those with poor prognosis and also found that the BIS value of 72hr and one week was significantly higher in the prognosis group than in the poor prognosis group, and was significantly correlated with the degree of brain resuscitation improvement or recovery. At the same time, BIS monitoring can be carried out in the patient's bedside, the index quantification, indicating that the BIS value can be used as a more practical and more convenient index for the evaluation of neurological function in coma patients.

II. Method And Result

In research studied total 28 patients under observation and data is collected which classified under Pittsburgh cerebral performance category (CPC 1 to 5). Patients defined as unconscious, unresponsive, or having a Glasgow coma scale score (GCS) ≤8 were considered as comatose in studies. Among them, 13 male patients, 15 female patients in the age between 48 to 92 years old, (72.10±11.35) years old. Majority of patients under Coronary disease, cardiomyopathy disease, pulmonary embolism or respiratory failure, hypertension and diabetes mellitus.

The tests result of patients classified according to Normal range of the tests and find-out that like in Liver/kidney functional test Normal levels of AST and ALT may slightly vary depending on the individual laboratory's reference values. Typically the range for normal AST is reported between 10 to 40 units per liter and ALT between 7 to 56 units per litre, while in research studies of 28 patients, majority of patients data comes under normal range of AST and ALT, which further classified under the group of CPC 1-3 and CPC 4-5. Moreover, The blood electrolytes test, blood sugar test and arterial blood gases test result mostly towards normal to medium level and classified under the group of CPC 1-3 and CPC 4-5 as show in table number 1

Index		Number of patients (28)	CPC1-3(11)	CPC4-5(17)	P Value
Age		72.12±11.35	60.36±6.46	79.7±5.94	<0.05
Gender (Male)		13/28	6/11	7/17	>0.05
Gcs (>8)		15/28	6/11	9/17	>0.05
Liver/ kidney functioning test (Normal range)					>0.05
AST	10-40u/l	21/28	7/11	14/17	
ALT	8-55u/l	4/28	3/11	1/17	
Blood Roution (Normal range)					>0.05
WBC	4,500 to 10,000 cells/mcl	16/28	7/11	9/17	
RBC	5to 6 million cells/mcl	14/28	6/11	8/17	
Plat.	140,000 to 450,000 cells/mcl	12/28	7/11	4/17	
Blood Sugar					>0.05
Normal range	4.0 to 5.4 mmol/L	5/28	3/11	2/17	
Electrolytes					>0.05
Na+	136-145 mmol/L	7/28	3/11	4/17	
K+	3.6-5.2mmol/L	10/28	6/11	4/17	
Arterial blood gases (Normal range)					>0.05
Po ₂ mmhg	54-95 mmhg	9/28	5/11	4/17	
Pco ₂ mmhg	80-100 mmHg	8/28	5/11	3/11	
Note- Good prognosis CPC1-3, Poor Prognosis -CPC4-5 , CPC(cerebral performance categories)					

2.2 Research Methods:

Patients were evaluated in terms of age, sex, duration of resuscitation efforts, Glasgow coma scale (GCS) score, pupillary reactivity to light, need of sedation, and time interval to blood sampling for NSE measurement. Resuscitation protocols followed American Heart Association guidelines⁽⁷⁸⁾. Every resuscitated patient was admitted to an intensive care unit and the care provided followed the routine of the units, without interference from the investigators.

The criteria for cerebral function change in coma patients were Rosc to maintain more than 24H. After collecting ROSC 24hr, 72hr and one week ,3 ML of peripheral venous blood (4,3 r/min centrifugation 5~ min) separating plasma, taking serum to detect NSE, using Roche cobas- automatic electrochemical chemiluminescence Immunoassay (Switzerland) to detect serum NSE. After ROSC, the patient was monitored by the BIS monitoring module of Philip Monitor, and the BIS value was recorded in 24hr, 72hr, and one week and three time-points respectively.

The BIS values were recorded and the serum NSE was measured at: 24 h, 72 h, and one week respectively after ICU admission. **Neurological outcome was classified according to the Pittsburgh cerebral performance category (CPC 1 to 5).** Poor neurological outcome was defined as a Cerebral Performance Category (CPC) of 4 to 5 (severe neurological disability, persistent vegetative state or death) as opposed to CPC 1–3 (absent, mild or moderate neurological disability). In studies CPC 4–5 was defined as a poor outcome. When original data were not available to correct outcome as CPC 3–5, a CPC 4–5 was accepted as a surrogate poor outcome, assigning the study an indirectness score. When the outcome was expressed using a modified Rankin Score (mRS) an equivalent CPC was calculated based on the equivalence $mRS \geq 4 = CPC \geq 3$

2.3 Statistical Analysis:Using SPSS 16.0 statistical software processing data, measurement data with **mean ± standard deviation (x±s)**, the comparison between groups using variance analysis, the rate of comparison use Fisher accurate probability method, NSE level and BIS value of the diagnostic effectiveness and limit values using **ROC curve Analysis**, and calculate the area under the curve. The difference of $P < 0.05$ was statistically significant.

In this research study used SPSS 16.0 for analysis the data of 28 coma patients and draw a ROC(Receiver operating characteristic) and find out a AUC (Area under curve) for validation of the result. Calculate True Positive Rate (TPR) or Sensitivity and True Negative Rate (TNR) or Specificity using ROC curve and formulate Cut-off value for the validation of the study. In study using Two parameter BIS and NES with variable include age and GCS for coma patients to evaluate the result and find out prognostic value of these parameter for positive result in the research.

III. Result

Patient data indicates BIS and NSE value (Mean± Standard variance)at 24hr,72hr and One week of all 28 patients which divided in two prognosis group CPC 1-3 and CPC 4-5 although, the prognosis of the group (cpc1-3) Age (60.36±6.46) is lower than the poor prognosis Group (cpc4-5) (79.7±5.94) ($P < 0.05$), and there was no statistically significant difference in age sex ratio.

BIS AND NSE VALUE AT 24HR, 72HR AND ONE WEEK IN TWO GROUP

(Mean± Standard variance)

Index	BIS (24 hr)	BIS (72 hr)	BIS (One week)	NSE (24 hr)	NSE (72hr)	NSE (One week)
CPC1-3(13)	58.63±12.10	68.3±14.2	84.18±13.2	63.5±27.1	53.2±19.6	46.1±20.7
CPC4-5(31)	53.76±14.27	56.7±25.5	63.1±27.3	71.2±39.6	87.7±49.5	96.3±42.1
P Value	>0.05	<0.01	<0.01	>0.05	<0.01	<0.05

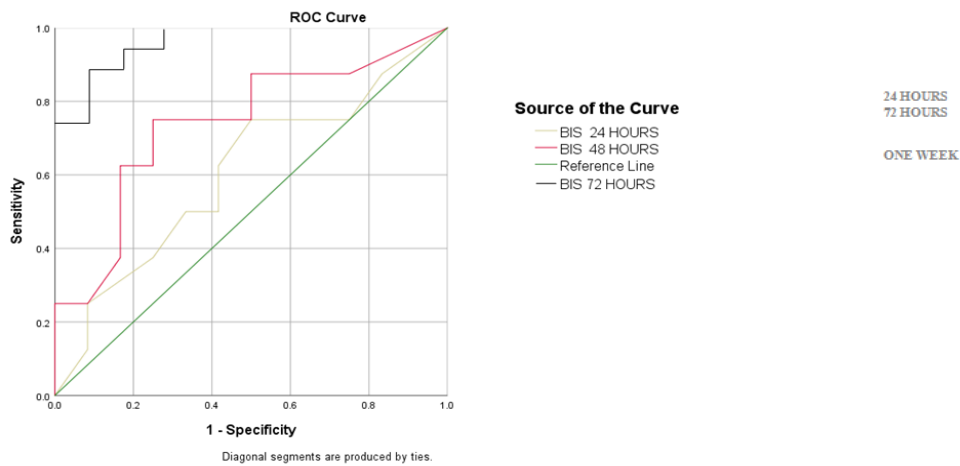
Note : NSE unit= ng/mL

Analysis outcome:

BIS values of 24h, 72h and one week BIS were recorded in two groups of patients, there was no statistically significant difference in the 24h BIS value of both groups [(Cpc1-3: (58.63±12.10) vs. Cpc4-5: (53.76±14.27)), the BIS value at 72 h of good prognosis group was higher than bad prognosis group [(cpc1-3: (68.3±14.2) vs. Cpc4-5: (56.7±25.5)) is significantly Higher ($P < 0.05$), and the BIS value at one week in good prognosis group was significantly higher than bad prognosis group [cpc1-3: 84.18±13.2] vs. Cpc4-5: (63.1±27.3)] ($P < 0.05$)

The BIScutoff value Value at 24h are40.50 ng/ml with Area under curve(AUD) is 0.604 and sensitivity 72%, specificity 85%.Whereas at 72 H, BIS cutt off values were 49.8 ng/ml and Area under curve is 0.74 with the sensitivity 82% and the specificity is 90% and at one week BIScutoff value are42.85 ng/ml with Area under curve(AUD) is 0.95 and sensitivity 86%, specificity 99%.

BIS VALUE AT 24, 72HR AND ONE WEEK

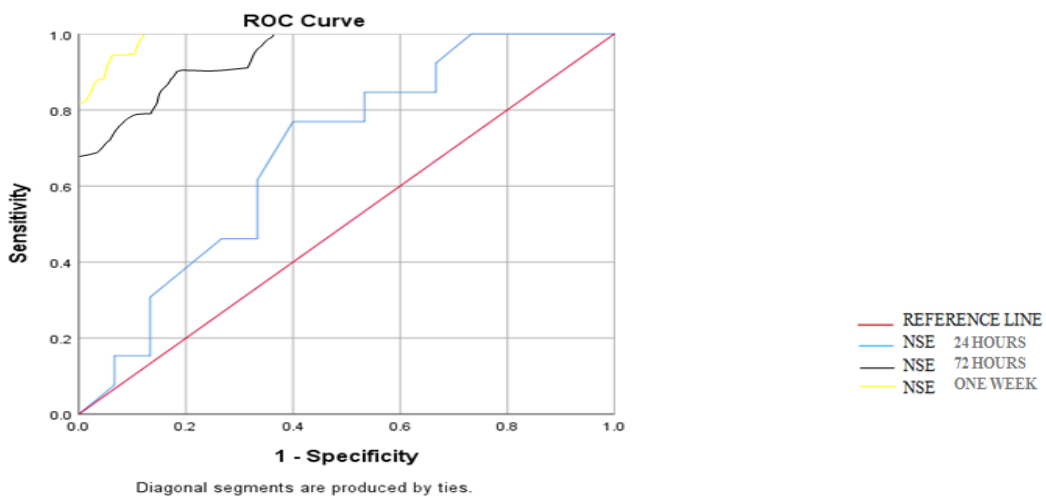


The ROC curve graphically displays the trade-off between sensitivity and specificity and is useful in assigning the best cut-offs for clinical use. Overall accuracy is sometimes expressed as area under the ROC curve (AUC) and provides a useful parameter for comparing test performance between At lower BNP cut-offs, e.g. 40.50 pg/mL, there is higher sensitivity or better ability to identify patients with brain resuscitation(BR), although this is compromised by lower specificity (i.e. the test falsely identifies more subjects without BR).

Higher sensitivity, however is higher negative predictive value, in other words the test performs better as a “rule-out” test and enables the clinician to consider causes of dyspnoea other than BR. Conversely, higher cut-offs are more likely to identify patients with BR than due to other causes, in other words higher specificity and positive predictive value, giving a better “rule-in” test. In study find out Bis cut-off Value at 24h, 72h and one week is 40.50, 49.8 and 42.85 ng/ml respectively and AUC value 0.604, 0.74 and **0.95** respectively and specificity increases upto 99% which give positive result for rule out.

NSE Value ,There was no significant change between the two groups under 24hours [(cpc1-3: (63.5±27.1) vs. Cpc4-5: (71.2±39.6)),after 72h, the prognosis of a good group of NSE significantly decreased ($P<0.05$) [(Cpc1-3: (52.2±19.6) vs. Cpc4-5: (87.7±49.5))after one week, the prognosis of a good group of NSE level is also lower than the prognosis of the poor group ($P<0.05$) [(Cpc1-3: (46.1±20.7 vs. cpc4-5 96.3 ± 37.0)),the cut-off value of NSE 47.62 ng/ml, sensitivity 79%, specificity 85%. In one week, NSE values were 38.6 ng/ml, the sensitivity degree is 86%, the specificity is 99% and AUC at 24, 48 and 72 hours is 0.59, 0. 83 and **0.98** respectively.

NSE VALUE AT 24HR, 72HR AND ONE WEEK



NSE cut-off Value at 24h, 72h and one week is 43.20, 47.62 and 38.6ng/ml respectively and AUC value 0.59,0.83 and **0.98**respectively.

In the Good Prognosis Group (table 4) The NSE value decreased significantly in both 72H and one week and the prognosis of the group was lower in the 72hour than 24 hours, NSE decreased (11.3±7.5) ng/ml, one week hour was lower than 72 hour (6.1±1.10) ng/ml. The value of NSE in the poor prognosis group showed an upward trend in the 72hour and one week, especially in the

patients with poor prognosis, the 72 H increased significantly in the 24H. The difference of NSE in two groups was statistically significant. The NSE value show prominent result for the analysis of the study outcome with upwards trend in lower group and downward trend in good group for NSE value. With the prognosis cut-off value specificity are increases in both groups from 24hours to one week which emphasis on the result.

NSE VALUE DIFFERENCE IN BOTH GROUPS

NSE	CPC 1-3	CPC 4-5	P Value
ΔNSE 24h~72h	(11.3±7.5)	16.5±9.9	<0.01
ΔNSE 72h~One week	(6.1±1.10)	8.6±2.5	<0.05
Note : NSE unit- ng/mL			

Finally, Sensitivity and specificity vary with the cut-off chosen for a diagnostic test and are not intrinsic to the test but critically dependent upon the clinical context. ROC curve analysis enables the best cut-off for clinical purpose to be assigned, higher sensitivity corresponding to high negative predictive value and the ideal property of a “rule-out” test.

IV. Discussion

The results showed that the 48h and 72h NSE levels in the patients with good prognosis were significantly lower than those with poor prognosis and alsofound that the BIS value of 48 and 72h was significantly higher in the prognosis group than in the poor prognosis group, and was **significantly correlated with the degree of brain resuscitation improvement or recovery**. At the same time, **BIS monitoring** can be carried out in the patient's bedside, the index quantification, indicating that **the BIS value can be used as a more practical and more convenient index for the evaluation of neurological function in coma patients**.

V. Conclusion

This study findout that combine use of serum NSE levels and BIS monitoring used for evaluate the neurological prognosis of **brain resuscitation in coma patients**. However, this study is a single-centre clinical study, the sample size is small, and its conclusion needs to be clarified by further evidence-based medicine.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest regarding this study.

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