Bispectral index as a predictor of unsalvageable traumatic brain injury

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ABSTRACT

**Primary Objective:** We aimed to assess the utility of bispectral index (BIS) monitoring to diagnose brain death (BD) in patients with severe traumatic brain injury (TBI).

**Research Design and methods:** A prospective observational study was conducted for patients with severe TBI between 2012 and 2014.

**Main outcomes And results:** This study included 62 patients with a mean age of 32.5 ± 10.5 years. Nine patients had BD on admission with a sustainable BIS value of 0. Fifty-three patients were not initially diagnosed with BD with BIS values of 2–56. Forty-four patients deteriorated to BD, and their respective BIS values progressively decreased to 0. Nine patients with mean BIS of 39.2 ± 9.0 recovered and were transferred to a specialized high dependency unit. BIS values showed positive correlation with the Glasgow Coma Score (GCS) on admission (r = 0.43, p = 0.001). Survivors had higher BIS values than those who were initially declared BD or those who died during the hospitalization course (p = 0.001).

**Conclusion:** BIS values have a significant correlation with initial GCS and can assist in the early detection of BD in patients with severe acute TBI. Further larger studies are needed to support our findings.

Method

A prospective observational study was conducted to include all patients with severe acute TBI (Glasgow Coma Score; GCS ≤ 8) who were admitted to the trauma ICU at Hamad General Hospital, between 2012 and 2014. The study included patients with severe coma resulted mainly from head injury, traumatic hypoxic brain damage or intracerebral haemorrhage [13]. Patients who developed coma due to other causes such as drug intoxication, septic shock or other reversible abnormalities were excluded from the study. All study subjects were continuously monitored for BIS during the ICU stay. Data included demographics, mechanism of injury, admission GCS, associated injuries, BIS levels, brain stem test, EEG, tracheostomy and outcome measures such as BD (on admission or later in the ICU) and survival (transfer to high dependency unit). Severe TBI was defined as patients with head Abbreviated Injury Score ≥ 3 and GCS ≤ 8. Patients were classified based on the outcome measures as already on-admission BD, patients not clinically BD on admission but...
later declared BD on the final assessment in ICU stay and those who survived (not BD) eventually transferred to long-term care.

In our study, the measurement of brain electrical activity was performed by the BIS-monitor system (Covidien, Gunbarrel Ave, Boulder, USA). BIS monitoring was recorded continuously for all patients during the ICU stay. The BIS sensor (BUS Quarto Sensor) was placed over the forehead of the patients which had four electrodes placed at an angle over the forehead of the patient. The first electrode was placed at the midline, around 5 cm above the nose; the second one was positioned inferior and lateral to the first electrode. The third electrode was placed behind the eye specifically on the temporal region of the head, and the fourth electrode was placed just above and adjacent to the eyebrow. Both physical examination and patients movements were carefully observed as these might interfere with the BIS monitoring which resulted in some neurological stimulation. Data were transferred and stored on the computer to be analysed by the EEG database algorithm which calculates numbers between 0 (translated as the absence of brain electrical activity) and 100 (fully awake and conscious).

Diagnostic criteria for BD: The diagnosis of BD was confirmed by the standard of care hospital criteria which include a systematic, thorough physical examination conducted by three physicians (consultant, specialist and neurologist) and revealed irreversible brain damage, unresponsive coma (no response to painful stimuli), absence of brain stem reflexes and an apnoea test consistent with BD. The clinical examination was performed in the absence of complicating conditions, such as drug intoxication or poisoning, neuromuscular blocking (relaxant) drugs, hypothermia (core temperature ≤36.5°C), and metabolic or endocrine disturbances. When necessary, the clinical BD was measured by other neurological examinations such as brain stem test and EEG to confirm the diagnosis. This study was conducted with the approval (IRB#12145/12) of the Medical Research Center at Hamad Medical Corporation, Doha, Qatar.

Data were presented as proportion, median (range), or mean (±standard deviation; SD) as appropriate. Pearson’s correlation coefficient was calculated between BIS values and admission GCS. The Mann–Whitney test was performed to compare the BIS values between BD and survived cases. The ANOVA test was performed for comparisons of the continuous variables in more than two groups. A significant difference was considered when the two-tailed p-value was less than 0.05. A data analysis was carried out using the Statistical Package for Social Sciences version 18 (SPSS Inc., Chicago, IL).

Results
During the study period, a total of 62 patients with severe TBI met the inclusion criteria. The mean age of the patients was 32.5 ± 10.5 years and the majority (98%) were males (Table 1). The most frequent mechanism of injury was motor vehicle crash (38.7%) followed by fall from height (35.5%). The face (27.5%), abdomen (22.5%) and chest (15%) were the commonly injured body regions. The mean GCS on admission to the trauma ICU was 3.8 ± 1.7. Figure 1

![Figure 1. Summary of the hospital course of severely comatose TBI patients.](image-url)
summarizes the course of the patients with severe TBI and in coma admitted to trauma ICU. Nine patients were BD on admission to ICU, and their respective BIS values were 0 and these levels remained 0 permanently. In these cases, the BD was diagnosed as per the standard criteria and confirmation was done either by brain stem test or EEG, if indicated. Fifty-three patients were not clinically BD at the time of admission to ICU and their BIS levels ranged between 2 and 56. During the course of ICU stay that varied from few hours to few days based on neurological status, 44 patients clinically deteriorated and were diagnosed to have BD, and their respective BIS values progressively decreased to 0. In these patients whose BIS values dropped to 0, other tests including brain stem test or EEG were performed to confirm the BD. The remaining nine patients did not develop BD during their ICU stay and their mean BIS value was 39.2 ± 9.0. All these nine patients recovered and were transferred to a specialized high dependency unit for long-term care. The BIS values showed a significant positive correlation with the GCS on admission to ICU (r = 0.43, p = 0.001). Moreover, the median BIS values of survivors were significantly higher than those who were declared BD [37 (30–56) vs. 5 (0–18); p = 0.001] (Figure 2). Table II shows the comparison among three groups of patients with severe TBI (BD who died on admission, not BD but died during the hospital course and not BD and transferred to rehabilitation services).

**Discussion**

BIS is one of the technologies that is being used primarily for monitoring the depth of anaesthesia in patients after mechanical ventilation or being sedated with the use of anaesthetic agents after trauma, surgery or critical illness. These patients are at an increased risk of morbidity and mortality, as they suffered from complex critical conditions, such as cerebrovascular disease, TBI, and cardiac dysfunction that require cardiopulmonary resuscitation [12]. Early detection of BD in such patients would help to prevent deterioration of the organs for donation and saving ICU resources [9]. Patients with BD develop sudden haemodynamic instability which is harmful to the organs and if delayed, further prevents organ donation [14]. Hence, the diagnosis and confirmation of BD should be made at an early stage. Recent studies have demonstrated the ability of BIS to be used for the diagnosis of BD among patients with severe coma admitted to the ICU [11,12].

The present study was conducted to assess the utility and accuracy of BIS monitoring as a clinical evaluation tool for the confirmation of BD in 62 patients post-severe TBI and in coma. In our series, all patients who were already diagnosed as BD on admission to ICU had BIS value of 0 and also patients clinically deteriorated to have BD later during ICU stay had BIS values that progressively decreased to 0. Viven et al. [11] conducted a prospective study of 56 severely comatose patients and reported findings similar to our cohort that

![Figure 2. Comparison of bispectral index (BIS) levels with the diagnosis of brain death (p = 0.001).](image)

| Table II. Comparison between brain dead (BD) and not brain dead (NBD) groups. |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| BD and died on admission(N = 9) | NBD on admission but died later (N = 44) | NBD on admission and transferred to Rehab (N = 9) | p    |
| Mean age, years | 29.6 ± 8 | 31.6 ± 10 | 39.9 ± 13 | 0.06 |
| Mean GCS scoring | 3.2 ± 0.7 | 3.6 ± 1.4 | 5 ± 2.4 | 0.03 |
| Mean BIS values | 0 | 5.14 ± 2.8 | 39 ± 9 | 0.001 |
patients diagnosed as BD on admission or later in the ICU had BIS values of 0. Therefore, the assessment of BD onset as indicated by the BIS value of 0 might be used as a potential threshold for early confirmation using EEG or cerebral angiography which will eventually help in identifying suitable candidates for organ donation and appropriate utilization of ICU resources.

Furthermore, those who survived in that study had an average BIS value of 35 which is in line with the mean BIS of 39 among those who did not become BD in our cohort. The current study addressed the utilization of prognostic value of BIS in TBI cases. Dou et al. [12] reported that BIS > 42.5 can potentially diagnose patients with conscious coma (mixed ICU patients) with high sensitivity and specificity. However, patients with TBI comprised only one-third of the cohort of Dou et al. and the severity of brain injury was not specified.

Moreover, patients who never progressed to BD during the ICU stay had higher BIS values than those who developed BD. Our findings are consistent with an earlier study by Viven et al. [11] suggesting that the onset of BD correlated with the BIS value of 0 among severe comatose patients in ICU. Also in our series, BIS accurately diagnosed BD which correlates well with the confirmatory investigation such as brain stem test. These observations were supported by other studies as well. An earlier study recommended the use of BIS monitoring at the onset of BD to enable the early scheduled use of other tests including EEG or cerebral angiography to confirm the diagnosis of BD [11]. Duo et al. [12] also demonstrated the efficacy of BIS to be used as a clinical tool for the prognosis of comatose patients in ICU. The authors suggested that BIS was inversely correlated with the mental status of these patients and recommended BIS monitoring as a useful clinical tool to determine the prognosis (either improvement or deterioration) of patients with severe coma.

Li et al. [15] studied the impact of BIS in 61 patients with acute brain injury. In that study, BIS was continuously monitored for 12 hours within the first 3 days or off sedative for 24 hours. The BIS mean value showed a positive correlation with GCS (r = 0.38, p = 0.003), but was inversely related to S100 protein biomarker (r = -0.42, p = 0.001). The authors concluded that BIS monitoring can be used as an early objective indicator to assess the prognosis of acute brain injury.

On the other hand, some studies suggested that BIS cannot be used solely for the conformation of BD; however, it should be coupled with other measures. One study by Escudero et al. [1] showed a correlation of the BD with BIS monitoring as all patients who have BIS level of 0 and suppression rest of 100 except one patient. In addition, the authors believed that BIS alone cannot be used to confirm the diagnosis of the disease; however, it can be used to detect the onset of BD. Another study by Schnakers et al. [8] recommended the combination of EEG with BIS recording to be an advatage for accurate diagnosis and prognosis of patients with severe TBI recovering from coma.

Moreover, in our series, BIS values showed a significant positive correlation with the lower GCS on admission to ICU and also patients declared BD later in the ICU had considerably lower BIS values which progressively decreased to BIS value of 0 on the onset of BD. Ebtehaj et al. [16] conducted a study on 61 consecutive patients with TBI which showed significant association between GCS and BIS values. The authors recommended the use of BIS monitoring in addition to GCS for the better prognosis.

A Korean study demonstrated a considerable relationship between the BIS values and the level of consciousness (GCS) in patients with severe TBI [17]. It has been suggested that BIS scores are more useful to predict the mental status of coma patients as compared to those with conscious coma or drowsiness. In line with the other findings, these investigators considered BIS monitoring as an adjunct with GCS or other neurological tests for the evaluation of consciousness levels [17]. Other studies on ischaemic hypoxic brain injury [18] and severe TBI [19] also suggested better chance of recovery based on the prediction of BIS levels.

Our previous work to investigate the clinical implications of BIS in multiple trauma patients [20] showed that BIS monitoring is useful to reduce agitation, extubation failure, and ICU stay. It has been observed that BIS values and GCS correlate well in patients with mild and moderate TBI [21]. Nevertheless, in such patients, the depth of coma cannot be assessed accurately by BIS monitoring due to higher degree of variability. Contrarily, another study assessed impairment of consciousness in patients visiting emergency department which observed a weak correlation between BIS and GCS. This could be explained by the fact that BIS and consciousness levels are assessed from different regions of the brain and may not necessarily corroborate with each other [17].

There are certain limitations in the present report. The relatively small sample size renders limited study power; however, all the patients who met the inclusion criteria were enrolled in the study and most recently published reports are based on similar sample size as our cohort or even less. Also, there is a possibility of BIS monitoring artefacts which might occur in patients with major intracranial hypertension which shows a decrease in BIS values to 0 prior to the onset of BD which might result in “Transient false positives”. Moreover, in some clinically BD patients, the BIS values falsely elevate for some time due to simultaneous increases in electromyography activity and cardiovascular hyperpulsatility which are referred as “Transient false negatives”. Therefore, it has been recommended to perform an assessment of the raw EEG waveform to overcome the paradoxical EEG delta rhythm and artefacts resulting in misleading BIS values [22]. In our cohort, the sample size might not allow a generalization of our results. However, we believe that this preliminary threshold BIS value which has been derived from smaller cohort would essentially help to optimize BIS cut-off to be used for prognostication. By using larger sample size, the sensitivity, specificity and predictive values can be obtained to find the cut-off of BIS that can initially predict the patients’ outcome.

In conclusion, BIS monitoring can be used as an adjunct assessment tool for the early detection of BD in patients with severe acute TBI. Even though, BIS is not an absolute assessment tool for the detection of BD, it is a simple, non-invasive device to be used at bedside for continuous monitoring of electrophysiological activity of brain to indicate early onset of
BD. Moreover, the BIS value shows a significant correlation with the GCS and other diagnostic modalities to confirm BD. However, further larger studies are needed to assess the potential of BIS monitoring to replace the EEG and cerebral angiography, and to optimize the BIS threshold for survival and for early diagnosis of BD in patients with severe acute TBI to be considered as potential candidates for organ transplantation. Further larger studies are also needed to support our findings and to find out the cut-off prognostic BIS value in these high-risk patients.

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Declaration of Interest

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