

# Brain death: Our experiences in intensive care unit

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## Abstract

**Aim:** The aim of this study was to examine patients retrospectively with brain death (BD) who were diagnosed in our intensive care unit (ICU).

**Material and Methods:** This retrospective descriptive study evaluated 24 patients with diagnosed BD in the ICU between January 2012 and December 2015 using digital patient records. We registered demographic, clinical and laboratory findings, Acute Physiology and Chronic Health Evaluation System (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, Glasgow Coma Score (GCS), development of complications, donation rate, time of BD diagnosis and length of ICU stay.

**Results:** Twenty-four patients (11 males, 13 females) with BD whose ages were between 24–83 years old. The etiologies of BD diagnosis were medical causes in 20 cases (83.3 %) and traumatic causes in 4 cases (16.7 %). Subarachnoid haemorrhage due to a cranial aneurysm was the most common cause of ICU admission (n = 6). The mean APACHE II score was  $16 \pm 5.2$ , GCS was  $4.25 \pm 2.5$ , and the SOFA score was  $8.4 \pm 3.5$  on ICU admission. The mean time of BD diagnosis was  $147.8 \pm 19$  hours and the mean length of ICU stay was  $8.8 \pm 7.7$  days. Confirmatory tests (cranial angiography, cranial Doppler, cranial CT angiography) were performed on 16 patients. The acceptance rate for organ donation was 45.8% (n = 11).

**Conclusion:** The intensivist should target to both confirm and declare the diagnosis of BD in the shortest time and increase the number of organs transplanted per donor.

**Keywords:** Brain Death; Donor Rate; Intensive Care Unit.

## INTRODUCTION

Death is an irreversible biological event that consists of permanent cessation of an organism's critical functions (1). At the end of the last century, a new definition of death was introduced. In the past, the irreversible loss of heart and lung functions had signalled death. The new definition was based on the irreversible loss of brain functions. The transition from the heart to the brain grew out of several parallel developments that converged in 1968 (2). Brain death is defined by a total and irreversible loss of brain, brainstem and cerebellar functions in a patient with a beating heart (3). In 1959, the concept of BD emerged from Mollaret and Goulon who described patients with irreversible coma. By the mid 1960s, the terms cerebral death syndrome and electrocerebral silence were used to identify such patients. In 1963, a triad of BD criteria included: fixed and dilated pupils, no elicitable reflexes and no spontaneous movements; apnoea and isoelectric electroencephalography (EEG). Those who met these

criteria could be considered death 'in spite of cardiac action' (2). In 1968, the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death issued a report that defined 'irreversible coma' as BD (4-6).

Briefly, the current BD criteria are irreversible coma, a positive apnea test and absence of brainstem reflexes on neurological examination. According to these criteria, there may be potential brain death patients currently waiting to be diagnosed in the ICU. We believe that awareness of the clinical features of BD among intensivists should be increased and early diagnosis of BD and donor care are very important issues. Donor care is the responsibility of the intensivist with both on-site and on-time diagnosis.

The aim of this study was to evaluate retrospectively the demographic characteristics, clinical features, laboratory findings, diagnoses, BD detection time, additional tests performed, family's organ donation rate, length of ICU stay and outcomes of adult patients with BD in our ICU.

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## MATERIAL and METHODS

This trial has been approved by the Research Ethics Committee and performed in accordance with accepted ethical standards (Ankara University Medical Faculty Clinical Research Ethics Committee, No:15-769-16, date: October 10<sup>th</sup>, 2016). Accordance to Helsinki Declaration, written informed consent was waived from parents of the patients. We retrospectively reviewed the data of 24 patients diagnosed with BD between January 2012 and December 2015. Data were recorded; demographic, clinical and laboratory findings of patients such as sex, age, APACHE II score, SOFA score, GCS, cause (s) of admission to the ICU, development of complications, donation rates, time of BD diagnosis and length of ICU stay. Data were obtained from digital records and files of patients.

### Brain death was diagnosed according to the following criteria:

- 1) Prerequisites including definite and irreversible coma not caused by the drug (s), hypothermia, alcohol and other abnormal laboratory values;
- 2) Examination indicating the absence of brainstem reflexes;
- 3) The apnea test result is positive and
- 4) Ancillary tests can be used when uncertain about the clinical examination or when the apnea test cannot be performed.

If the result of the first three criteria were positive, a repeat determination was performed 12 h later for these patients. If a confirmatory test was performed and supported BD on the first examination, the second neurological examination was not done (7). Brain death was diagnosed by two physicians: one of whom was a neurologist or neurosurgeon, and the other was an anesthesiologist or intensivist. Before the apnea test, an initial arterial blood gas sample was obtained to establish baseline PaCO<sub>2</sub> levels, disconnection of mechanical ventilation from the patient, followed by insertion of a catheter or cannula into the endotracheal tube down to the level of the carina, through which oxygen was delivered. Oxygen flow was usually 4–10 L min<sup>-1</sup>. A positive apnea test was determined by the rapid increase in PaCO<sub>2</sub> to 60 mmHg or a 20 mmHg increase in PaCO<sub>2</sub> over baseline normal PaCO<sub>2</sub> and the absence of any respiratory effort under these conditions. A negative test was defined by any spontaneous respiratory efforts in response to hypercapnic/acidotic stimulation (8).

A vasopressor agent may be required due to hemodynamic instability (mean systolic arterial pressure < 65 mmHg) in patients after BD. Vasopressor agents were noradrenaline, adrenaline, dopamine and/or dobutamine. Vasopressor, desmopressin and insulin therapy were used intravenously.

We analyzed laboratory values of patients at hospital admission and after the diagnosis of BD in the study. Laboratory values were blood urea nitrogen (BUN), creatinine, sodium, potassium, aspartate aminotransferase

(AST), alanin aminotransferase (ALT), hemoglobin, hematocrit, platelet, prothrombin time (PT), international normalized ratio (INR), D-dimer.

### Statistical Analysis

The Statistical Package for Social Sciences 22.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis. Data were analysed as number (n), per cent (%), minimum-maximum value and mean ± standard deviation (SD). Laboratory values of patients at hospital admission and after the diagnosis of BD were compared using a paired t-test for continuous variables. A p-value <0.05 was considered as statistically significant.

## RESULTS

Twenty-four patients, 13 females and 11 males, were included in this study and were diagnosed brain death between January 2012 and December 2015. The mean age was 45 ± 14 years (between 24 and 83 years). All patients were definite coma and excluded diseases due to drug, hypothermia and alcohol. Three patients (12.5%) were referred to the ICU from the emergency clinic, 4 patients (16.7%) from another centre and 17 (70.8%) from other clinics within our institution. The etiologies of BD diagnosis were medical causes in 20 cases (83.3%) and traumatic causes in 4 cases (16.7%). The causes of coma were aneurysmal subarachnoid hemorrhage (6 patients, 25%), spontaneous intracerebral hemorrhage (5 patients, 20.8%), cerebral ischaemia (4 patients, 16.6%), brain tumours (3 patients, 12.5%), hypertensive subarachnoid hemorrhage (3 patients, 12.5%), traumatic subarachnoid hemorrhage (2 patients, 8.3%) and hypoxic-ischaemic encephalopathy (1 patient, 4.2%). The initial APACHE II score was 16 ± 5.2, GCS was 4.25 ± 2.5, and SOFA score was 8.4 ± 3.5 at ICU admission. An ap-nea test was attempted in 23 patients and was not done in 1 patient because of hemodynamic instability. While performing the apnea test, in 2 patients hypotension and 2 other patients hypoxemia occurred; hence the apnea test could not be completed in 4 patients. The diagnosis of BD was confirmed with ancillary tests in 16 patients. Since neurological examination could not be performed in 2 patients because of maxillofacial trauma, we could not evaluate brainstem reflexes. In addition, in 4 patients an apnea test could not be completed because of hypoxemia and hypotension during the apnea test. Also, in 1 patient the apnea test was not performed because of hemodynamic instability, and in 9 patients, who were admitted to our ICU from other clinics, were received for consideration of the diagnosis of BD. The ancillary test was fourvessel cerebral angiography, which was conducted in 8 patients (33.3%). This test was followed by computed tomography (CT) with cerebral angiography in 4 patients, and transcranial Doppler in the other 4 patients (16.7%). The mean time of BD evaluations was 147.8 ± 195 hours (min: 10, max: 738). The mean time of survival after the diagnosis of BD was 57.5 ± 92.7 hours (min: 4, max: 358). The mean time of diagnosis of BD from suspected BD 41.5 ± 43.1 hours (min: 6, max: 87). The mean length of stay in the ICU was 8.8 ± 7.7 days (min: 1, max: 31).

Complications after the declaration of BD include diabetes insipidus in 17 patients (70.8%), brain edema in 6 patients (25%) and hyperglycaemia in 1 patient (4.2%). When 16 (66.7%) cases were admitted to the ICU, a vasopressor agent was required because of hemodynamic instability; desmopressin treatment was required in 9 cases (37.5%) because of diabetes insipidus, and insulin was required in 6 cases (25%). After the diagnosis of BD, there was an increase in the number of patients who needed vasopressor (21 patients), desmopressin (11 patients) and insulin (10 patients) medication (Table 1). The diagnosis of BD was communicated to families of all patients.

Cardiac arrest occurred in 5 patients (21%) when waiting for their parents' donation decision, 8 families (33%) refused to donate organs, and 11 families (46%) approved the donation. Laboratory values of patients at hospital admission were compared with those after the diagnosis of BD. This comparison revealed that levels of potassium (K+) ( $p= 0.04$ ) and aspartate aminotransferase (AST) ( $p= 0.038$ ) increased whereas those of hemoglobin ( $p= 0.00$ ) and hematocrit ( $p= 0.00$ ) decreased; both of these results were statistically significant (Table 2).

**Table 1. Comparison of requirement of vasopressor, desmopressin and insulin treatments on admission at ICU and after diagnosis of BD**

Treatment requirement	On admission at ICU (n/%)		After diagnosis of BD (n/%)	
	Yes	No	Yes	No
Vasopressor	16 (66.7)	8 (33.3)	21 (87.5)	3 (12.5)
Desmopressin	9 (37.5)	15 (62.5)	11 (45.8)	13 (54.2)
Insulin	6 (25)	18 (75)	10 (41.7)	14 (58.3)

ICU: Intensive Care Unit, BD: Brain Death

**Table 2. Comparison of laboratory values on admission at ICU and diagnosis of brain death**

Laboratory value	Admission at ICU (mean $\pm$ SD)	Diagnosis time of BD (mean $\pm$ SD)
BUN (mg/dl)	17 $\pm$ 9.8	29.8 $\pm$ 39.1
Creatinine (mg/dl)	1.05 $\pm$ 0.37	1.48 $\pm$ 1.57
Sodium (mEq/L)	145.5 $\pm$ 9.5	148.5 $\pm$ 10
Potassium (mEq/L)**	3. $\pm$ 0.62	3.98 $\pm$ 0.91
AST (IU/L)**	81.8 $\pm$ 170.4	108.9 $\pm$ 176.4
ALT (IU/L)	51.7 $\pm$ 82.2	77.3 $\pm$ 103.4
Hemoglobin (mg/dl)**	11.9 $\pm$ 2.2	10.1 $\pm$ 2.27
Hematocrit (%)**	35.8 $\pm$ 6,3	30.7 $\pm$ 6.5
Platelet (mm <sup>3</sup> )	179.500 $\pm$ 72.200	222.500 $\pm$ 153.800
PT (sec)	18.5 $\pm$ 13.7	14.8 $\pm$ 4.11
INR	1.6 $\pm$ 1.18	1.29 $\pm$ 0.37
D- dimer (ng/dl)	3795.3 $\pm$ 5566.3	3487.2 $\pm$ 3693.5

\*\*Statistical significance was considered as a p value <0.05 between groups. ICU: In-tensive Care Unit, BD: Brain Death, BUN: Blood Urea Nitrogen, AST: Aspartate Ami-notransferase, ALT: Alanin Aminotransferase, PT: Prothrombin Time INR: International Normalized Ratio SD: Standard Deviation

## DISCUSSION

The diagnosis of BD is a clinical diagnosis that has incorporated three steps, which are the patient's comatous condition, is due to irreversible brain damage of known etiology and potentially reversible causes such as drug effects, metabolic or en-docrine issues or hypothermia must be excluded, absence of brainstem reflexes on neurological examination and a positive apnea test. Brain death is the complete and irre-versible loss of cerebral and brainstem function. In most countries and most situa-tions, BD is considered equivalent to cardiopulmonary death. The diagnosis of BD has important medical, ethical and legal implications, because it may entail the withdrawal of all life-sustaining measures or the recovery of organs for transplanta-tion. The diagnosis of BD is based on clinical examination, in accordance with interna-tional standards nevertheless, under certain clinical conditions, ancillary testing might also be necessary (1,2-4).

The first criterion is the comatose condition because of irreversible brain damage of known etiology and severe head trauma, aneurysmal subarachnoid hemorrhage and intracerebral hemorrhage are the most common events leading to BD. In the present study, the rate of medical causes was 83%, and the most common medical cause of BD was aneurysmal subarachnoid hemorrhage (25%). According to two studies in the literature, trauma was identified as the most common cause in Turkey (9,10) and other studies have reported that intracranial hemorrhage as the most common cause (8-11,12). In our institution, general trauma patients were followed in the department of neurosurgery. Therefore, it was determined that patients who had BD because of medical reasons were more likely to be diagnosed with trauma than those diagnosed with trauma. All categories of brain injury were of high severity on admission to the ICU. The mean GCS was  $4.25 \pm 2.5$ . These findings are similar to the results of many studies (11-13). Three patients (12.5%) were referred to the ICU from the emergency room, 4 patients (16.7%) from another centre and 17 (70.8%) from within our institution. The number of patients who were accepted from the emergency depart-ment is similar in 2 studies in the literature (14,15). Sixteen patients with suspicion of BD, therefore, started the diagnostic process with radiological imaging were admitted to tertiary ICU. Clinicians believed that these cases should be diagnosed BD so that they could be organ donors and needed donor care. Donor management is a fundamental situation for organ donation. Hence, cases who are candidates to donate require close and advanced hemodynamic monitoring, appropriate fluid replacement therapy and mechanical ventilation. For these reasons, these patients should be followed in the tertiary ICU. In this study, 10 patients (41.7%) required decompressive surgery because of increased intracranial pressure during the followup period. In Saxicki et al.'s study, 26 (31%) of patients underwent decompressive craniectomy before the diagnosis of BD (12). When the full clinical examination, including both assessments of brainstem reflexes and the apnea test, is performed conclusively, no additional testing

is required to determine BD. For a diagnosis of BD, ancillary testing is conducted if patient factors prohibit both a complete clinical examination and apnea test. Conventional brain angiography is the gold standard method for the diagnosis of BD; CT angiography, which is a faster and noninvasive procedure, is an alternative method; and transcranial Doppler is another imaging method that examines basilar and middle cerebral arteries and depends on the operator. In a Spanish clinical trial, both EEG and Doppler are the most commonly used tests (16). In our study, four-vessel cerebral angiography was the first choice test and the second most common techniques are CT angiography and transcranial Doppler. In the United Kingdom, confirmatory tests are not required but may be useful to reduce any element of uncertainty or minimise the period of observation before the diagnosis of brainstem death if preconditions for clinical testing are unsatisfied, or a comprehensive neurological examination is unfeasible (17). In Turkey when a patient is not appropriate to perform a neurological examination or the apnea test because of maxillofacial trauma or hemodynamic instability, the intensivist may prefer to perform an ancillary test. In the present study, a neurological examination could not be performed in 2 patients because maxillofacial trauma precluded the evaluation of brainstem reflexes; in 4 patients an apnea test could not be completed because hypoxemia and hypotension occurred during the apnea test; in 1 patient the apnea test was not performed because of hemodynamic instability; and in 9 patients, who were admitted to our ICU from other clinics, were received for consideration for diagnosis of BD. For these reasons, BD was confirmed by cerebral angiography in 8 cases, CT angiography in 4 cases and patient transcranial Doppler in 4 cases. Donor care of patients before and after the determination of BD is necessary to optimise organ recovery, donation and increase the number of organs transplanted per donor. During the period of BD diagnosis and waiting for donation several complications may occur. Therefore, the time of the BD diagnosis is an essential issue so that critical care specialists should be on the alert while the patient is followed up in the ICU. According to outcomes in this study, the mean time of BD diagnosis was  $147.8 \pm 195$  hours (range, between 10 and 738 hours). Kiraklı et al. reported this time as 7 hours and Güzeldağ et al. reported it as 48–384 hours (15,9). According to a meta-analysis, BD was diagnosed at a mean time of  $3.2 \pm 0.4$  days after recovery of circulation [18]. Our outcome was longer than other studies' outcomes, but we thought that cases in this study who did not resuscitate from cardiac arrest were followed up for intracranial pathology such as traumatic brain injury, hypertensive subarachnoid hemorrhage (SAH) and brain tumour. First, cases were admitted to be treated in the ICU. The mean length of stay in ICU was  $8.8 \pm 7.7$  days. The duration of ICU stay was determined to be between 3 and 21 days by Guzeldag et al. (9). After the diagnosis of BD, the mean duration of stay in the ICU was  $57.5 \pm 92.7$  hours and after this time cardiac arrest occurred. The mean duration of diagnosis of BD from

suspected BD was  $41.5 \pm 43.1$  hours. While increasing awareness of BD diagnosis and simultaneously improving donor care, the organ transplantation rate has increased. According to the Global Observatory on Donation and Transplantation (GODT) statistics, in 2016 in Turkey, the total number of organ transplantations was 4921 (61.8%), and 562 (7.06%) of them had been taken at BD from individuals who were cadaveric donors. Also, Spain has the highest donor rate in the world (16,19). According to the Republic of Turkey Ministry of Health, Directorate General of Health Services statistics, in 2017, the total number of BDs was 2042, and 554 of them were organ donors but 25,111 patients are awaiting an organ transplant. Therefore, the diagnosis of BD is gradually increasing (20,21). The part of BD declaration is the most difficult part of making the diagnosis of BD. The diagnosis of BD was declared to all patients' families. Eleven patients' families (45.8%) approved donation and all of them were suitable for organ donation. In a systemic review, the informed rate of organ donation among brain dead patients was 41.8% (18). Our donation outcome was lower when compared with Turkey's outcome. We thought that there were many underlying causes such as ethnical differences, migration issues, religious beliefs and socioeconomic circumstances. In two studies that had been done in our country, this rate was found to be 88% and 74%, respectively (13,14). Vander Hoeven et al. evaluated organ functions and serum parameters of rats with BD that were stable and unstable hemodynamically. Serum parameters were higher in the unstable group. Brain death is a dynamic state and organs progressively lose functions (22). In our study, the increase in potassium and AST and the decrease in hemoglobin and hematocrit at the time of diagnosis of BD were both statistically significant. Brain death culminates in a cascade of events leading to severe cardiovascular instability secondary to central sympatholysis, a profound pro-inflammatory state and hormonal dysregulation. Endocrine changes in BD occur secondary to both anterior and posterior pituitary injury from ischaemia, direct compression, or both. These are variable in both timing and severity, and result in hypothyroidism, adrenal insufficiency and diabetes insipidus (DI). Insulin concentrations also decrease after BD leading to hyperglycaemia. Evidence suggests that hormone replacement therapy in donation after BD (DBD) donors increases the number of organs suitable for transplantation (23). In 46%–78% of cases of BD, DI is reported and should be treated with a vasopressin infusion or desmopressin (24). Twenty-one patients (87.5%) diagnosed with BD required vasopressor treatment and the requirement for vasopressor, desmopressin and insulin therapy increased after the diagnosis of BD.

This investigation was a retrospective study from a single centre, and the sample size was small, but we only considered demographic, clinical characteristics of patients and developing complications and reported our experience in BD.

## CONCLUSION

In conclusion, while critical care specialists make an 'end-of-life decision' for someone, at the same time they make a 'beginning of a new life decision' for another person. This situation is a difficult decision not only for intensivists but also for family members of patients. Therefore, all clinicians must consider legal, ethical and medical issues during this period. In addition to these matters, intensivists should focus on confirming and making the diagnosis of BD in the shortest time to maximise the number of organs transplanted per donor.

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